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* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	JAN 02	STN pricing information for 2008 now available
NEWS	3	JAN 16	CAS patent coverage enhanced to include exemplified prophetic substances
NEWS	4	JAN 28	USPATFULL, USPAT2, and USPATOLD enhanced with new custom IPC display formats
NEWS	5	JAN 28	MARPAT searching enhanced
NEWS	6	JAN 28	USGENE now provides USPTO sequence data within 3 days of publication
NEWS	7	JAN 28	TOXCENTER enhanced with reloaded MEDLINE segment
NEWS	8	JAN 28	MEDLINE and LMEDLINE reloaded with enhancements
NEWS	9	FEB 08	STN Express, Version 8.3, now available
NEWS	10	FEB 20	PCI now available as a replacement to DPCI
NEWS	11	FEB 25	IFIREF reloaded with enhancements
NEWS	12	FEB 25	IMSPRODUCT reloaded with enhancements
NEWS	13	FEB 29	WPINDEX/WPIDS/WPIX enhanced with ECLA and current U.S. National Patent Classification
NEWS	14	MAR 31	IFICDB, IFIPAT, and IFIUDB enhanced with new custom IPC display formats
NEWS	15	MAR 31	CAS REGISTRY enhanced with additional experimental spectra
NEWS	16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
NEWS	17	MAR 31	LPCI now available as a replacement to LDPCI
NEWS	18	MAR 31	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	19	APR 04	STN AnaVist, Version 1, to be discontinued
NEWS	20	APR 15	WPIDS, WPINDEX, and WPIX enhanced with new predefined hit display formats
NEWS	21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS	22	APR 28	IMSRESEARCH reloaded with enhancements

NEWS EXPRESS FEBRUARY 08 CURRENT WINDOWS VERSION IS V8.3,
AND CURRENT DISCOVER FILE IS DATED 20 FEBRUARY 2008

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:51:25 ON 26 MAY 2008

=> microfluidic and red blood cells
MICROFLUIDIC IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s microfluidic and red blood cells
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
command can only be used to look at the index in a file which has an
index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
commands which can be used in this file.

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.42       0.42

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
       CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 17:52:32 ON 26 MAY 2008

69 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s microfluidic and red blood cells
          9   FILE ANABSTR
          1   FILE ANTE
          8   FILE BIOENG
         28   FILE BIOSIS
          1   FILE BIOTECHABS
          1   FILE BIOTECHDS
          1   FILE BIOTECHNO
          3   FILE CABA
         57   FILE CAPLUS
          1   FILE CEABA-VTB
  23 FILES SEARCHED...
          7   FILE DISSABS
         31   FILE EMBASE
         25   FILE ESBIOBASE
         65   FILE IFIPAT
          8   FILE LIFESCI
         37   FILE MEDLINE
          1   FILE NTIS
         15   FILE PASCAL
  48 FILES SEARCHED...
          1   FILE PHIN
          8   FILE PROMT
         66   FILE SCISEARCH
          4   FILE TOXCENTER
        580   FILE USPATFULL
        113   FILE USPAT2
         25   FILE WPIDS
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         25   FILE WPINDEX

  26 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L1   QUE MICROFLUIDIC AND RED BLOOD CELLS

=> s cell(p)size and cell(p)bind? and L1
          0*  FILE ADISNEWS
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE BIOENG
          0*  FILE BIOTECHABS
          0*  FILE BIOTECHDS
          0*  FILE BIOTECHNO
  13 FILES SEARCHED...
          2   FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
  23 FILES SEARCHED...
          0*  FILE ESBIOBASE
          0*  FILE FOMAD
          0*  FILE FOREGE
          0*  FILE FROSTI
          0*  FILE FSTA
  36 FILES SEARCHED...
         18   FILE IFIPAT
          0*  FILE KOSMET
          1   FILE MEDLINE
          0*  FILE NTIS
          0*  FILE NUTRACEUT
          0*  FILE PASCAL
          0*  FILE PHARMAML
  53 FILES SEARCHED...
        255   FILE USPATFULL
         49   FILE USPAT2
          0*  FILE WATER
          3   FILE WPIDS
          3   FILE WPINDEX

   7 FILES HAVE ONE OR MORE ANSWERS,   69 FILES SEARCHED IN STNINDEX

L2   QUE CELL(P) SIZE AND CELL(P) BIND? AND L1

=> file caplus ifipat medline uspatfull uspat2
COST IN U.S. DOLLARS                        SINCE FILE      TOTAL
                                               ENTRY    SESSION
FULL ESTIMATED COST                             4.55       4.97

FILE 'CAPLUS' ENTERED AT 17:56:56 ON 26 MAY 2008
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FILE 'IFIPAT' ENTERED AT 17:56:56 ON 26 MAY 2008
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FILE 'MEDLINE' ENTERED AT 17:56:56 ON 26 MAY 2008

FILE 'USPATFULL' ENTERED AT 17:56:56 ON 26 MAY 2008
CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 17:56:56 ON 26 MAY 2008
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CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l2
L3 325 L2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 259 DUP REM L3 (66 DUPLICATES REMOVED)

=> s L4 and enrich?
L5 163 L4 AND ENRICH?

=> s l5 and hist
L6 0 L5 AND HIST

=> s l5 and bind?
L7 163 L5 AND BIND?

=> s l7 and obstacle?
L8 70 L7 AND OBSTACLE?

=> s l8 and binding to obstacle?
L9 0 L8 AND BINDING TO OBSTACLE?

=> s l8 and microfluidic device
L10 19 L8 AND MICROFLUIDIC DEVICE

=> d l10 1-19

L10 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2004:292081 CAPLUS
DN 140:283937
TI Microfluidic device for cell separation and uses thereof
IN Toner, Mehmet; Truskey, George; Kapur, Ravi
PA The General Hospital Corporation, USA; GPB Scientific LLC
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004029221	A2	20040408	WO 2003-US30965	20030929
	WO 2004029221	A3	20040513		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2500392	A1	20040408	CA 2003-2500392	20030929
	AU 2003277153	A1	20040419	AU 2003-277153	20030929
	EP 1569510	A2	20050907	EP 2003-798803	20030929
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006501449	T	20060112	JP 2004-540301	20030929
	US 20060134599	A1	20060622	US 2005-529453	20051219

	US 20070172903	A1	20070726	US 2007-726230	20070321
	US 20070231851	A1	20071004	US 2007-726276	20070321
	US 20070259424	A1	20071108	US 2007-726231	20070321
	US 20070264675	A1	20071115	US 2007-800940	20070508
PRAI	US 2002-414065P	P	20020927		
	US 2002-414102P	P	20020927		
	US 2002-414258P	P	20020927		
	WO 2003-US30965	W	20030929		
	US 2005-529453	A3	20051219		

L10 ANSWER 2 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11614553 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007264675 A1 20071115
AI US 2007-800940 20070508
RLI US 2005-529453 20051219 CONTINUATION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007264675 20071115
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 16 Nov 2007
Last Updated on STN: 13 Dec 2007
CLMN 27
GI 25 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

FIG. 7 is a schematic diagram of a cell binding device.

FIG. 8 is an exploded view of a cell binding device.

FIG. 9 is an illustration of obstacles in a cell binding device.

FIG. 10 is an illustration of types of obstacles.

FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

FIG. 18 is an illustration of a method of fabricating a cell binding device.

FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L10 ANSWER 3 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11609304 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007259424 A1 20071108
AI US 2007-726231 20070321
RLI US 2005-529453 20051219 DIVISION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)

US 2002-414258P 20020927 (Provisional)
FI US 2007259424 20071108
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 14 Nov 2007
Last Updated on STN: 13 Dec 2007
CLMN 34
GI 25 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

FIG. 7 is a schematic diagram of a cell binding device.

FIG. 8 is an exploded view of a cell binding device.

FIG. 9 is an illustration of obstacles in a cell binding device.

FIG. 10 is an illustration of types of obstacles.

FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 1 6B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log

with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.
FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.
FIG. 18 is an illustration of a method of fabricating a cell binding device.
FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.
FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.
FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.
FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.
FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.
FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.
FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells
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L10 ANSWER 4 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11581736 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007231851 A1 20071004
AI US 2007-726276 20070321
RLI US 2005-529453 20051219 CONTINUATION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007231851 20071004
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 8 Oct 2007
Last Updated on STN: 9 Nov 2007
CLMN 32
GI 25 Figure(s).
FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.
FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.
FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.
FIG. 4 is an illustration of the outlet channels of the device.
FIG. 5 is an illustration of a device for cell lysis.
FIGS. 6A and 6B are illustrations of a method for the fabrication of a

device of the invention.
FIG. 7 is a schematic diagram of a cell binding device.
FIG. 8 is an exploded view of a cell binding device.
FIG. 9 is an illustration of obstacles in a cell binding device.
FIG. 10 is an illustration of types of obstacles.
FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.
FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.
FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.
FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.339 l. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.
FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.
FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.
FIG. 18 is an illustration of a method of fabricating a cell binding device.
FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.
FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.
FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.
FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.
FIG. 23 is an illustration of a cell binding device in

which beads trapped in a hydrogel are used to capture cells.
FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.
FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells
.
Figures are not necessarily to scale.

L10 ANSWER 5 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11522821 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007172903 A1 20070726
AI US 2007-726230 20070321
RLI US 2005-529453 20051219 DIVISION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007172903 20070726
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 26 Jul 2007
Last Updated on STN: 16 Aug 2007
CLMN 44
GI 25 Figure(s).
FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.
FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.
FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.
FIG. 4 is an illustration of the outlet channels of the device.
FIG. 5 is an illustration of a device for cell lysis.
FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.
FIG. 7 is a schematic diagram of a cell binding device.
FIG. 8 is an exploded view of a cell binding device.
FIG. 9 is an illustration of obstacles in a cell binding device.
FIG. 10 is an illustration of types of obstacles.
FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.
FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array
FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.
FIG. 14A is a graph of the overall efficiency as a function of pressure

drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

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FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L10 ANSWER 6 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11376372 IFIPAT;IFIUDB;IFICDB
TI DEVICES AND METHODS FOR ENRICHMENT AND ALTERATION OF CELLS AND OTHER PARTICLES
IN Barber Thomas A; Carvalho Bruce L; Huang Lotien Richard; Kapur Ravi; Toner Mehmet; Vernucci Paul; Wang Zihua
PA Unassigned Or Assigned To Individual (68000)
PI US 2007026381 A1 20070201
AI US 2006-449149 20060608
RLI WO 2006-US12820 20060405 CONTINUATION PENDING
PRAI US 2005-668415P 20050405 (Provisional)
US 2005-704067P 20050729 (Provisional)

FI US 2007026381 20070201
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
ED Entered STN: 2 Feb 2007
    Last Updated on STN: 20 Mar 2007
CLMN 116
GI 68 Figure(s).

FIGS. 1A-1E are schematic depictions of an array that separated cells based on deterministic lateral displacement: (A) illustrates the lateral displacement of subsequent rows; (B) illustrates how fluid flowing through a gap is divide unequally around obstacles in subsequent rows; (C) illustrates how a particle with a hydrodynamic size above the critical size is displaced laterally in the device; (D) illustrates an array of cylindrical obstacles; and (E) illustrates an array of elliptical obstacles.

FIG. 2 is a schematic description illustrating the unequal division of the flux through a gap around obstacles in subsequent rows.

FIG. 3 is a schematic depiction of how the critical size depends on the flow profile, which is parabolic in this example.

FIG. 4 is an illustration of how shape affects the movement of particles through a device.

FIG. 5 is an illustration of how deformability affects the movement of particles through a device.

FIG. 6 is a schematic depiction of deterministic lateral displacement. Particles having a hydrodynamic size above the critical size move to the edge of the array, while particles having a hydrodynamic size below the critical size pass through the device without lateral displacement

FIG. 7 is a schematic depiction of a three-stage device.

FIG. 8 is a schematic depiction of the maximum size and cut-off size (i.e., critical size) for the device of FIG. 7.

FIG. 9 is a schematic depiction of a bypass channel.

FIG. 10 is a schematic depiction of a bypass channel.

FIG. 11 is a schematic depiction of a three-stage device having a common bypass channel.

FIG. 12 is a schematic depiction of a three-stage, duplex device having a common bypass channel.

FIG. 13 is a schematic depiction of a three-stage device having a common bypass channel, where the flow through the device is substantially constant.

FIG. 14 is a schematic depiction of a three-stage, duplex device having a common bypass channel, where the flow through the device is substantially constant.

FIG. 15 is a schematic depiction of a three-stage device having a common bypass channel, where the fluidic resistance in the bypass channel and the adjacent stage are substantially constant.

FIG. 16 is a schematic depiction of a three-stage, duplex device having a common bypass channel, where the fluidic resistance in the bypass channel and the adjacent stage are substantially constant.

FIG. 17 is a schematic depiction of a three-stage device having two, separate bypass channels.

FIG. 18 is a schematic depiction of a three-stage device having two, separate bypass channels, which are in arbitrary configuration.

FIG. 19 is a schematic depiction of a three-stage, duplex device having three, separate bypass channels.

FIG. 20 is a schematic depiction of a three-stage device having two, separate bypass channels, wherein the flow through each stage is substantially constant.

FIG. 21 is a schematic depiction of a three-stage, duplex device having three, separate bypass channels, wherein the flow through each stage is substantially constant.

FIG. 22 is a schematic depiction of a flow-extracting boundary.
FIG. 23 is a schematic depiction of a flow-feeding boundary.
FIG. 24 is a schematic depiction of a flow-feeding boundary, including a bypass channel.
FIG. 25 is a schematic depiction of two flow-feeding boundaries flanking a central bypass channel.
FIG. 26 is a schematic depiction of a device having four channels that act as on-chip flow resistors.
FIG. 27 and 28 are schematic depictions of the effect of on-chip resistors on the relative width of two fluids flowing in a device.
FIG. 29 is a schematic depiction of a duplex device having a common inlet for the two outer regions.
FIG. 30A is a schematic depiction of a multiple arrays on a device. FIG. 30B is a schematic depiction of multiple arrays with common inlets and product outlets on a device.
FIG. 31 is a schematic depiction of a multi-stage device with a small footprint.
FIG. 32 is a schematic depiction of blood passing through a device.
FIG. 33 is a graph illustrating the hydrodynamic size distribution of blood cells.
FIGS. 34A-34D are schematic depictions of moving a particle from a sample to a buffer in a single stage (A), three-stage (B), duplex (C), or three-stage duplex (D) device.
FIG. 35A is a schematic depiction of a two-stage device employed to move a particle from blood to a buffer to produce three products. FIG. 35B is a schematic graph of the maximum size and cut off size of the two stages.
FIG. 35C is a schematic graph of the composition of the three products.
FIG. 36 is a schematic depiction of a two-stage device for alteration, where each stage has a bypass channel.
FIG. 37 is a schematic depiction of the use of fluidic channels to connect two stages in a device.
FIG. 38 is a schematic depiction of the use of fluidic channels to connect two stages in a device, wherein the two stages are configured as a small footprint array.
FIG. 39A is a schematic depiction of a two-stage device having a bypass channel that accepts output from both stages. FIG. 39B is a schematic graph of the range of product sizes achievable with this device.
FIG. 40 is a schematic depiction of a two-stage device for alteration having bypass channels that flank each stage and empty into the same outlet.
FIG. 41 is a schematic depiction of a device for the sequential movement and alteration of particles.
FIG. 42A is a photograph of a device of the invention. FIGS. 42B43E are depictions the mask used to fabricate a device of the invention. FIG. 42F is a series of photographs of the device containing blood and buffer.
FIGS. 43A-43F are typical histograms generated by the hematology analyzer from a blood sample and the waste (buffer, plasma, red blood cells, and platelets) and product (buffer and nucleated cells) fractions generated by the device of FIG. 42.
FIGS. 44A-44D are depictions the mask used to fabricate a device of the invention.
FIGS. 45A-45D are depictions the mask used to fabricate a device of the invention.
FIG. 46A is a micrograph of a sample enriched in fetal red blood cells. FIG. 46B is a micrograph of maternal red blood cell waste.
FIG. 47 is a series of micrographs showing the positive identification of male fetal cells (Blue=nucleus, Red=X chromosome, Green=Y chromosome).
FIG. 48 is a series of micrographs showing the positive identification of sex and trisomy 21.
FIGS. 49A-49D are depictions the mask used to fabricate a device of the

invention.
FIGS. 50A-50G are electron micrographs of the device of FIG. 49.
FIGS. 51A-51D are depictions the mask used to fabricate a device of the invention.
FIGS. 52A-52F are electron micrographs of the device of FIG. 51.
FIGS. 53A-53F are electron micrographs of the device of FIG. 45.
FIGS. 54A-54D are depictions the mask used to fabricate a device of the invention.
FIGS. 55A-55S are electron micrographs of the device of FIG. 54.
FIGS. 56A-56C are electron micrographs of the device of FIG. 44.
FIG. 57 is a flowchart describing the isolation of fetal red blood cell nuclei.
FIG. 58 is a schematic graph of the course of lysis of cells in a maternal blood sample.
FIG. 59 is a schematic diagram of a microfluidic method to enrich the cells of interest and preferentially lyse the cells of interest in the enriched sample. The sample is first enriched by size-based direction of cells of interest into a preferred channel, and the cells of interest are then selectively lysed by controlling their residence time in a lysis solution.
FIG. 60 is a schematic diagram of a microfluidic method of sizebased isolation of the nuclei of the lysed cells of interest from non-lysed whole cells of non-interest The cells of noninterest are directed into the waste, while the nuclei are retained in the desired product streams.
FIG. 61 is a flowchart describing an alternate method for the separation of fetal nuclei from maternal white blood cells.
FIG. 62 is a schematic diagram of a device of the invention employing a substantially constant gap width and flow-feeding and flow-extracting boundaries.
FIG. 63a is a schematic depiction of a manifold of the invention. FIG. 63b is a photograph of a manifold of the invention.
FIG. 64 is a graph of the percentage of viable cells as a function of exposure to a hypotonic lysis solution.
FIG. 65 is a graph of hemolysis of whole blood as a function of time in a lysis buffer.
FIG. 66a is a table that illustrates the nuclei recovery after Cytospin using Carney's fix solution total cell lysis procedure as described herein.
FIG. 66b is a series of fluorescent micrographs showing an example of nuclei FISH results using Carney's fix mediated total cell lysis. The nuclei are FISHed for X (aqua), Y (green) and Y (red) and counterstained with DAPI.
FIG. 67 is a flowchart detailing various options for lysis of cells and nuclei.

L10 ANSWER 7 OF 19 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11185565 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA Unassigned Or Assigned To Individual (68000)
PPA General Hospital Corp The (Probable)
PI US 2006134599 A1 20060622
AI US 2003-529453 20030929
WO 2003-US30965 20030929
20051219 PCT 371 date
20051219 PCT 102(e) date
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2006134599 20060622

DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 24 Jun 2006
Last Updated on STN: 24 Jun 2006
CLMN 69
GI 32 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

FIG. 7 is a schematic diagram of a cell binding device.

FIG. 8 is an exploded view of a cell binding device.

FIG. 9 is an illustration of obstacles in a cell binding device.

FIG. 10 is an illustration of types of obstacles.

FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%.

FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array.

FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop.

FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr.

FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10

target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

FIG. 18 is an illustration of a method of fabricating a cell binding device.

FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series.

FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention.

FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation.

FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L10 ANSWER 8 OF 19 USPATFULL on STN
AN 2008:130394 USPATFULL
TI SELECTION OF CELLS USING BIOMARKERS
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Wang, Zihua, Newton, MA, UNITED STATES
PI US 2008113358 A1 20080515
AI US 2007-830546 A1 20070730 (11)
PRAI US 2006-820778P 20060728 (60)
DT Utility
FS APPLICATION
LN.CNT 3370
INCL INCLM: 435 6
NCL NCLM: 435 6
IC IPCI C12Q0001-68 [I,A]

L10 ANSWER 9 OF 19 USPATFULL on STN
AN 2008:76951 USPATFULL
TI DC-dielectrophoresis microfluidic apparatus, and applications of same
IN Li, Dongqing, Antioch, TN, UNITED STATES
PA Vanderbilt University, Nashville, TN, UNITED STATES (U.S. corporation)
PI US 2008067068 A1 20080320
AI US 2006-523782 A1 20060919 (11)
DT Utility
FS APPLICATION
LN.CNT 2209
INCL INCLM: 204/451.000
INCLS: 204/601.000
NCL NCLM: 204/451.000

NCLS: 204/601.000
IC IPCI C07K0001-26 [I,A]; C07K0001-00 [I,C*]; G01N0027-00 [I,A]
IPCR C07K0001-00 [I,C]; C07K0001-26 [I,A]; G01N0027-00 [I,C];
G01N0027-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 10 OF 19 USPATFULL on STN
AN 2007:68534 USPATFULL
TI System for size based separation and analysis
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley MT, MA, UNITED STATES
Huang, Lotion R., Brookline, MA, UNITED STATES
Barber, Tom, Cambridge, MA, UNITED STATES
Carvalho, Bruce, Watertown, MA, UNITED STATES
Gray, Darren, Brookline, MA, UNITED STATES
PI US 2007059781 A1 20070315
AI US 2005-229336 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2363
INCL INCLM: 435/007.210
INCLS: 435/287.200; 702/019.000
NCL NCLM: 435/007.210
NCLS: 435/287.200; 702/019.000
IC IPCI G01N0033-567 [I,A]; G06F0019-00 [I,A]; C12M0003-00 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; C12M0003-00 [I,C];
C12M0003-00 [I,A]; G06F0019-00 [I,C]; G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 11 OF 19 USPATFULL on STN
AN 2007:68527 USPATFULL
TI Kits for Prenatal Testing
IN Grisham, Michael, Richmond, VA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
PI US 2007059774 A1 20070315
AI US 2005-229037 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2316
INCL INCLM: 435/007.200
NCL NCLM: 435/007.200
IC IPCI G01N0033-567 [I,A]; G01N0033-53 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; G01N0033-53 [I,C];
G01N0033-53 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 12 OF 19 USPATFULL on STN
AN 2007:68473 USPATFULL
TI Business methods for prenatal Diagnosis
IN Grisham, Michael, Richmond, VA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Tompkins, Ron, Boston, MA, UNITED STATES
Schmidt, Martin, Reading, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059719 A1 20070315
AI US 2005-229332 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2356
INCL INCLM: 435/006.000
INCLS: 705/002.000

NCL NCLM: 435/006.000
NCLS: 705/002.000
IC IPCI C12Q0001-68 [I,A]; G06Q0050-00 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06Q0050-00 [I,C];
G06Q0050-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 13 OF 19 USPATFULL on STN
AN 2007:68472 USPATFULL
TI Systems and methods for enrichment of analytes
IN Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059718 A1 20070315
AI US 2005-229328 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2296
INCL INCLM: 435/006.000
INCLS: 435/069.100
NCL NCLM: 435/006.000
NCLS: 435/069.100
IC IPCI C12Q0001-68 [I,A]; C12P0021-06 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12P0021-06 [I,C];
C12P0021-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 14 OF 19 USPATFULL on STN
AN 2007:68470 USPATFULL
TI Methods for detecting fetal abnormality
IN Balis, Ulysses, Peabody, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
Walsh, John, Auburndale, MA, UNITED STATES
PI US 2007059716 A1 20070315
AI US 2005-228454 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2300
INCL INCLM: 435/006.000
INCLS: 702/020.000
NCL NCLM: 435/006.000
NCLS: 702/020.000
IC IPCI C12Q0001-68 [I,A]; G06F0019-00 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06F0019-00 [I,C];
G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 15 OF 19 USPATFULL on STN
AN 2007:68437 USPATFULL
TI Veterinary diagnostic system
IN Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien R., Brookline, MA, UNITED STATES
Gray, Darren, Brookline, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059683 A1 20070315
AI US 2005-229359 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2321
INCL INCLM: 435/005.000
INCLS: 435/006.000; 435/007.200; 977/902.000; 977/924.000
NCL NCLM: 435/005.000

NCLS: 435/006.000; 435/007.200; 977/902.000; 977/924.000
IC IPCI C12Q0001-70 [I,A]; C12Q0001-68 [I,A]; G01N0033-567 [I,A];
G01N0033-53 [I,A]
IPCR C12Q0001-70 [I,C]; C12Q0001-70 [I,A]; C12Q0001-68 [I,C];
C12Q0001-68 [I,A]; G01N0033-53 [I,C]; G01N0033-53 [I,A];
G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 16 OF 19 USPATFULL on STN
AN 2007:68434 USPATFULL
TI System for cell enrichment
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Huang, Lotien R., Brookline, MA, UNITED STATES
PI US 2007059680 A1 20070315
AI US 2005-228462 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2356
INCL INCLM: 435/004.000
INCLS: 435/005.000; 435/287.100; 435/006.000
NCL NCLM: 435/004.000
NCLS: 435/005.000; 435/006.000; 435/287.100
IC IPCI C12Q0001-00 [I,A]; C12Q0001-70 [I,A]; C12Q0001-68 [I,A];
C12M0003-00 [I,A]
IPCR C12Q0001-00 [I,C]; C12Q0001-00 [I,A]; C12M0003-00 [I,C];
C12M0003-00 [I,A]; C12Q0001-68 [I,C]; C12Q0001-68 [I,A];
C12Q0001-70 [I,C]; C12Q0001-70 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 17 OF 19 USPATFULL on STN
AN 2004:292265 USPATFULL
TI Microfluidic particle-analysis systems
IN Daridon, Antoine, Belmont, CA, UNITED STATES
PA Fluidigm Corporation, South San Francisco, CA, 94080 (U.S. corporation)
PI US 2004229349 A1 20041118
AI US 2003-640510 A1 20030812 (10)
RLI Continuation-in-part of Ser. No. US 2003-405092, filed on 31 Mar 2003,
ABANDONED
PRAI US 2002-369538P 20020401 (60)
US 2002-378464P 20020506 (60)
DT Utility
FS APPLICATION
LN.CNT 6326
INCL INCLM: 435/305.200
NCL NCLM: 435/305.200
IC [7]
ICM C12M001-22
IPCI C12M0001-22 [ICM,7]
IPCR G01N0037-00 [I,C*]; G01N0037-00 [I,A]; B01L0003-00 [I,C*];
B01L0003-00 [I,A]; C12M0001-00 [I,C*]; C12M0001-00 [I,A];
C12M0001-34 [I,C*]; C12M0001-34 [I,A]; C12M0003-00 [I,C*];
C12M0003-00 [I,A]; C12N0001-00 [I,C*]; C12N0001-00 [I,A];
C12Q0001-02 [I,C*]; C12Q0001-02 [I,A]; G01N0015-02 [N,C*];
G01N0015-02 [N,A]; G01N0015-14 [I,C*]; G01N0015-14 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 18 OF 19 USPATFULL on STN
AN 2004:286218 USPATFULL
TI Microfluidic particle-analysis systems
IN Chou, Hou-Pu, Sunnyvale, CA, UNITED STATES
Daridon, Antoine, Belmont, CA, UNITED STATES

Farrell, Kevin, San Francisco, CA, UNITED STATES
Fowler, Brian, Foster City, CA, UNITED STATES
Liau, Yish-Hann, San Jose, CA, UNITED STATES
Manger, Ian D., San Francisco, CA, UNITED STATES
Nassef, Hany Ramez, San Mateo, CA, UNITED STATES
Throndset, William, San Francisco, CA, UNITED STATES
PA Fluidigm Corp., South San Francisco, CA, UNITED STATES (U.S. corporation)
PI US 2004224380 A1 20041111
AI US 2003-734963 A1 20031211 (10)
RLI Continuation of Ser. No. US 2003-405953, filed on 1 Apr 2003, PENDING
PRAI US 2002-369538P 20020401 (60)
US 2002-378464P 20020506 (60)
DT Utility
FS APPLICATION
LN.CNT 6605
INCL INCLM: 435/029.000
INCLS: 435/288.500; 422/068.100; 436/063.000
NCL NCLM: 435/029.000
NCLS: 422/068.100; 435/288.500; 436/063.000
IC [7]
ICM G01N033-00
ICS C12M001-34; C12Q001-02
IPCI G01N0033-00 [ICM,7]; C12M0001-34 [ICS,7]; C12Q0001-02 [ICS,7]
IPCR B01L0003-00 [I,C*]; B01L0003-00 [I,A]; G01N0015-02 [N,C*]; G01N0015-02 [N,A]; G01N0015-14 [I,C*]; G01N0015-14 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L10 ANSWER 19 OF 19 USPATFULL on STN
AN 2004:94825 USPATFULL
TI Microfluidic particle-analysis systems
IN Chou, Hou-Pu, Sunnyvale, CA, UNITED STATES
Daridon, Antoine, Belmont, CA, UNITED STATES
Farrell, Kevin, San Francisco, CA, UNITED STATES
Fowler, Brian, Foster City, CA, UNITED STATES
Liau, Yish-Hann, San Jose, CA, UNITED STATES
Manger, Ian D., San Francisco, CA, UNITED STATES
Nassef, Hany Ramez, San Mateo, CA, UNITED STATES
Throndset, William, San Francisco, CA, UNITED STATES
PA Fluidigm Corporation, South San Francisco, CA (U.S. corporation)
PI US 2004072278 A1 20040415
US 7312085 B2 20071225
AI US 2003-405953 A1 20030401 (10)
PRAI US 2002-369538P 20020401 (60)
US 2002-378464P 20020506 (60)
DT Utility
FS APPLICATION
LN.CNT 6606
INCL INCLM: 435/029.000
INCLS: 422/068.100; 436/063.000; 435/288.500
NCL NCLM: 436/043.000; 435/029.000
NCLS: 422/050.000; 422/068.100; 422/081.000; 422/082.000; 422/100.000; 422/101.000; 422/102.000; 422/103.000; 422/104.000; 435/004.000; 435/325.000; 435/382.000; 435/383.000; 435/384.000; 435/404.000; 435/405.000; 436/063.000; 436/180.000; 435/288.500
IC [7]
ICM G01N033-00
ICS C12M001-34; C12Q001-02
IPCI G01N0033-00 [ICM,7]; C12M0001-34 [ICS,7]; C12Q0001-02 [ICS,7]
IPCI-2 G01N0035-00 [I,A]; G01N0033-48 [I,A]; G01N0001-10 [I,A]; G01N0015-06 [I,A]; G01N0033-00 [I,A]
IPCR G01N0035-00 [I,C]; G01N0035-00 [I,A]; B01L0003-00 [I,C*];

B01L0003-00 [I,A]; G01N0001-10 [I,C]; G01N0001-10 [I,A];
G01N0015-02 [N,C*]; G01N0015-02 [N,A]; G01N0015-06 [I,C];
G01N0015-06 [I,A]; G01N0015-14 [I,C*]; G01N0015-14 [I,A];
G01N0033-00 [I,C]; G01N0033-00 [I,A]; G01N0033-48 [I,C];
G01N0033-48 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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L19 NOT FOUND
The L-number entered has not been defined in this session, or it
has been deleted. To see the L-numbers currently defined in this
session, enter DISPLAY HISTORY at an arrow prompt (=>).

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L10 ANSWER 19 OF 19 USPATFULL on STN
AB The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or detection of particles, such as cells and/or beads. The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or analysis of particles, such as cells, viruses, organelles, beads, and/or vesicles. The invention also provides microfluidic mechanisms for carrying out these manipulations and analyses. These mechanisms may enable controlled input, movement/positioning, retention/localization, treatment, measurement, release, and/or output of particles. Furthermore, these mechanisms may be combined in any suitable order and/or employed for any suitable number of times within a system. Accordingly, these combinations may allow particles to be sorted, cultured, mixed, treated, and/or assayed, among others, as single particles, mixed groups of particles, arrays of particles, heterogeneous particle sets, and/or homogeneous particle sets, among others, in series and/or in parallel. In addition, these combinations may enable microfluidic systems to be reused. Furthermore, these combinations may allow the response of particles to treatment to be measured on a shorter time scale than was previously possible. Therefore, systems of the invention may allow a broad range of cell and particle assays, such as drug screens, cell characterizations, research studies, and/or clinical analyses, among others, to be scaled down to microfluidic size. Such scaled-down assays may use less sample and reagent, may be less labor intensive, and/or may be more informative than comparable macrofluidic assays.

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L10 ANSWER 19 OF 19 USPATFULL on STN
TI Microfluidic particle-analysis systems
AB The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or detection of particles, such as cells and/or beads. The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or analysis of particles, such as cells, viruses, organelles, beads, and/or vesicles. The invention also provides microfluidic mechanisms for carrying out these manipulations and analyses. These mechanisms may enable controlled input, movement/positioning, retention/localization, treatment, measurement, release, and/or. . . heterogeneous particle sets, and/or homogeneous particle sets, among others, in series and/or in parallel. In addition, these combinations may enable microfluidic systems to be reused. Furthermore, these combinations may allow the response of

particles to treatment to be measured on a shorter time scale than was previously possible. Therefore, systems of the invention may allow a broad range of cell and particle assays, such as drug screens, cell characterizations, research studies, and/or clinical analyses, among others, to be scaled down to microfluidic size. Such scaled-down assays may use less sample and reagent, may be less labor intensive, and/or may be more informative than. . .

PARN . . . and therein. This application further claims priority under 35 U.S.C. .sctn.120 as a continuation-in-part of the non-provisional patent application titled "Microfluidic Particle-Analysis Systems", by Chou et al., filed on Mar. 31, 2003 (Atty. Docket No.: 139F.310US), which is hereby incorporated by. . .

SUMM [0004] The invention relates to systems for the manipulation and/or detection of particles. More particularly, the invention relates to microfluidic systems for the manipulation and/or detection of particles, such as cells and/or beads.

SUMM [0007] The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or detection of particles, such as cells and/or beads.

DRWD . . . 1 is a flow chart showing potential temporal relationships between method steps for manipulation and/or detection of particles in a microfluidic system, in accordance with aspects of the invention.

DRWD [0009] FIG. 2A is a top plan view of a microfluidic system for retaining and analyzing a subset of input particles, in accordance with aspects of the invention.

DRWD [0010] FIG. 2B is a top plan view of another microfluidic system for retaining and analyzing a subset of input particles, in accordance with aspects of the invention.

DRWD [0011] FIG. 3 is a fragmentary, top plan view of yet another microfluidic system for retaining and analyzing a subset of input particles, in accordance with aspects of the invention.

DRWD [0013] FIG. 5 is a fragmentary, top plan view of a microfluidic system for positioning and retaining a group of particles, and for perfusing the retained group with selected reagents, in accordance. . .

DRWD [0020] FIG. 11A is a fragmentary, top plan view of a microfluidic system for measuring cell-cell communication, based on a duplicated version of the system of FIG. 8, in accordance with aspects. . .

DRWD . . . 11C is a top plan view of a two-dimensional array of particle capture chambers that may be used in a microfluidic system, in accordance with aspects of the invention.

DRWD [0023] FIG. 12 is a fragmentary, top plan view of a microfluidic system for retaining and perfusing two sets of particles in parallel, in accordance with aspects of the invention.

DRWD [0025] FIG. 13A is a top plan view of a microfluidic system for retaining two particles at spaced sites in a channel and perfusing the retained particles with distinct reagents, in. . .

DRWD [0036] FIG. 13L is a fragmentary, top plan view of a microfluidic system having separately addressable sets of linear trap arrays, in accordance with aspects of the invention.

DRWD [0037] FIG. 14 is a top plan view of a microfluidic system for retaining an array of particles in series and for perfusing members of this array separately and in parallel,. . .

DRWD [0040] FIG. 17 is a fragmentary, top plan view of a microfluidic device for forming an array of single particles or groups of particles, in accordance with aspects of the invention.

DRWD [0041] FIG. 18 is a pair of fragmentary, top plan schematic views of a microfluidic device for forming an array of retained particles that may be transferred to an array of separate sites, illustrating particle retention. . .

DRWD [0042] FIG. 19 is a pair of fragmentary, top plan schematic views of another microfluidic device for forming an array of retained particles that may be transferred to an array of separate sites, illustrating particle retention. . .

DRWD [0043] FIG. 20 is fragmentary, top plan schematic view of yet another microfluidic device for forming an array of retained particles that may be transferred to an array of separate sites, in accordance with. . .

DRWD [0044] FIG. 21 is a composite of top plan and sectional views showing selected portions of a microfluidic system for retaining particles using a particle-retention chamber that is fully spaced from the floor of the system, in accordance. . .

DRWD . . . FIG. 22 is a composite of top plan and sectional views, and a photographic image, showing selected portions of a microfluidic system for retaining particles using a particle-retention chamber that is partially spaced from the floor of the system, in accordance. . .

DRWD . . . FIG. 23 is a composite of top plan and sectional views, and two photographic images, showing selected portions of another microfluidic system for retaining particles using a particle-retention chamber that is fully spaced from the floor of the system, in accordance. . .

DRWD [0047] FIG. 24 is a fragmentary, top plan view of a reusable microfluidic system for repeated retention, treatment, and release of single particles, in accordance with aspects of the invention.

DRWD [0049] FIG. 26 is a fragmentary, top plan view of a reusable microfluidic system for repeated retention, treatment, and release of groups of particles, in accordance with aspects of the invention.

DRWD [0054] FIG. 31 is a top plan view of a microfluidic system having a sorting mechanism based on centrifugal force, in accordance with aspects of the invention.

DRWD [0056] FIG. 33 is a fragmentary, top plan view of another microfluidic system having a sorting mechanism based on centrifugal force, in accordance with aspects of the invention.

DRWD [0057] FIG. 34 is a top plan view of a yet another microfluidic system having a sorting mechanism based on centrifugal force, in accordance with aspects of the invention.

DRWD [0062] FIGS. 39-43 are top plan composite views of various cell-chamber networks for microfluidic manipulation of cells, in accordance with aspects of the invention.

DRWD [0063] FIG. 44 is a top plan view of a microfluidic system with a parallel array of separate, isolatable cell-chamber networks, in accordance with aspects of the invention.

DRWD [0064] FIG. 45 is a top plan view of a microfluidic system with an isolatable cell chamber that may be fed or bypassed by a parallel fluidic circuit, in accordance with. . .

DRWD [0065] FIG. 46 is a top plan view of a microfluidic system having a cell chamber that forms a loop, in accordance with aspects of the invention

DRWD [0066] FIG. 47 is a top plan view of a microfluidic system in which particle and reagent networks intersect at a common cell chamber, in accordance with aspects of the invention.

DRWD [0071] FIG. 50C is a top plan view of a cell chamber having two distinct compartments connected by a set of radially arrayed, size-selective channels, in accordance with aspects of the invention.

DRWD [0073] FIG. 51 is an isometric schematic view of a microfluidic system for performing electrophysiological analysis on an array of cells, in accordance with aspects of the invention.

DRWD [0074] FIG. 52 is a top plan view of a microfluidic system for performing electrophysiological analysis on a single cell, in accordance

with aspects of the invention.

DRWD [0075] FIG. 53 is a fragmentary top plan view of a microfluidic system related to the system of FIG. 52, showing a modified focusing mechanism, in accordance with aspects of the invention.

DRWD [0081] FIG. 59 is an abstracted view of a microfluidic device for performing patch-clamp analysis of cells, in accordance with aspects of the invention.

DRWD [0082] FIG. 60 is a fragmentary top plan view of a microfluidic device for performing patch-clamp analysis of multiple individual cells, in accordance with aspects of the invention.

DRWD [0084] FIG. 62 is a fragmentary side elevation view of a microfluidic mold spin-coated with a first layer of patternable, selectively removable material, in accordance with aspects of the invention.

DRWD . . . and measured signal plus noise without (top) and with (bottom) implementation of the modulation-demodulation method of FIG. 71B in a microfluidic system, in accordance with aspects of the invention.

DRWD . . . intensity versus time prior to and during cycles of exposure of a biotinylated bead to a streptavidin-dye conjugate in a microfluidic system, in accordance with aspects of the invention.

DRWD . . . ionomcyin to a retained cell that was preloaded with a calcium-sensor dye, using the method of FIG. 71B in a microfluidic system, in accordance with aspects of the invention.

DRWD [0099] FIG. 71F is a graph of measured fluorescence intensity versus time at a position in a microfluidic system prior to and during exposure to a dye, in accordance with aspects of the invention.

DRWD [0100] FIG. 72 is a time-lapse set of photographic images recording size-selective flow of blood cells through a microfluidic system, in accordance with aspects of the invention.

DRWD [0101] FIG. 73 is diagram showing the structure of biotin and its mode of binding to streptavidin.

DRWD [0102] FIG. 74 is a time-lapse set of photographic images recording interaction of specific binding pairs on beads in a microfluidic system, in accordance with aspects of the invention.

DRWD [0103] FIG. 75 is a time-lapse set of photographic images recording stimulation of ion flux in a microfluidic system, in accordance with aspects of the invention.

DRWD [0104] FIG. 76 is a time-lapse set of photographic images recording apoptosis and necrosis in a microfluidic system, in accordance with aspects of the invention.

DRWD [0106] FIG. 79 is a photographic image recording successful staining of a cell's membrane in a non-microfluidic environment.

DRWD . . . 80 is a time-lapse set of photographic images recording retention of a single cell at a preselected site in a microfluidic system, in accordance with aspects of the invention.

DRWD . . . is a time-lapse set of photographic images recording retention of a group of cells at a preselected site in a microfluidic system, in accordance with aspects of the invention.

DRWD [0110] FIG. 83 is a time-lapse set of photographic images recording fixation and staining of a retained cell in a microfluidic system, in accordance with aspects of the invention.

DRWD [0111] FIG. 84 is a top plan view of a microfluidic system for analyzing a size-selected set of cells, in which the system includes serially disposed filtration and retention mechanisms, a. . .

DRWD [0112] FIG. 85 is another top plan view of the microfluidic system of FIG. 84, showing identifying labels for reservoirs and valves, in accordance with aspects of the invention.

DETD [0119] The invention provides systems, including apparatus, methods, and kits, for the microfluidic manipulation and/or analysis of particles, such as cells, viruses, organelles, beads, and/or vesicles. The invention also provides microfluidic mechanisms for carrying out these manipulations and analyses. These mechanisms may enable controlled input, movement/positioning, retention/localization, treatment, measurement, release, and/or. . . heterogeneous particle sets, and/or homogeneous particle sets, among others, in series and/or in parallel. In addition, these combinations may enable microfluidic systems to be reused. Furthermore, these combinations may allow the response of particles to treatment to be measured on a shorter time scale than was previously possible. Therefore, systems of the invention may allow a broad range of cell and particle assays, such as drug screens, cell characterizations, research studies, and/or clinical analyses, among others, to be scaled down to microfluidic size. Such scaled-down assays may use less sample and reagent, may be less labor intensive, and/or may be more informative than. . .

DETD [0120] Further aspects of the invention are described in the following sections: (I) microfluidic systems, (II) physical structures of fluid networks, (III) particles, (IV) input mechanisms, (V) positioning mechanisms, (VI) retention mechanisms, (VII) treatment. . .

DETD [0121] Microfluidic Systems

DETD [0123] Particle manipulations and analyses are performed in microfluidic systems. A microfluidic system generally comprises any system in which very small volumes of fluid are stored and manipulated, generally less than about 500 μL, typically less than about 100 μL, and more typically less than about 10 μL. Microfluidic systems carry fluid in predefined paths through one or more microfluidic passages. A microfluidic passage may have a minimum dimension, generally height or width, of less than about 200, 100, or 50 μm. Passages. . .

DETD [0124] Microfluidic systems may include one or more sets of passages that interconnect to form a generally closed microfluidic network. Such a microfluidic network may include one, two, or more openings at network termini, or intermediate to the network, that interface with the external world. Such openings may receive, store, and/or dispense fluid. Dispensing fluid may be directly into the microfluidic network or to sites external the microfluidic system. Such openings generally function in input and/or output mechanisms, described in more detail in Sections IV and X below,. . .

DETD [0125] Microfluidic systems also may include any other suitable features or mechanisms that contribute to fluid, reagent, and/or particle manipulation or analysis. For example, microfluidic systems may include regulatory or control mechanisms that determine aspects of fluid flow rate and/or path. Valves and/or pumps that may participate in such regulatory mechanisms are described in more detail below in Section II. Alternatively, or in addition, microfluidic systems may include mechanisms that determine, regulate, and/or sense fluid temperature, fluid pressure, fluid flow rate, exposure to light, exposure to electric fields, magnetic field strength, and/or the like. Accordingly, microfluidic systems may include heaters, coolers, electrodes, lenses, gratings, light sources, pressure sensors, pressure transducers, microprocessors, microelectronics, and/or so on. Furthermore, each microfluidic system may include one or more features that act as a code to identify a given system. The features may. . .

DETD [0127] Microfluidic systems may be formed of any suitable material or combination of suitable materials. Suitable materials may include elastomers, such as. . .

DETD [0128] Exemplary materials for microfluidic systems are described in more detail in the patent applications listed above under Cross-References, which are incorporated herein by reference.

DETD [0130] Microfluidic systems, also referred to as chips, may have any suitable structure. Such systems may be fabricated as a unitary structure. . .

DETD . . . substantially planar layer that functions as a substrate layer, in some cases contributing a floor portion to some or all microfluidic passages.

DETD [0132] Components of a microfluidic system may be fabricated by any suitable mechanism, based on the desired application for the system and on materials used. . . material by micromachining, etching, soft lithography, material deposition, cutting, and/or punching, among others. Alternatively, or in addition, components of a microfluidic system may be fabricated without a mold by etching, micromachining, cutting, punching, and/or material deposition.

DETD [0133] Microfluidic components may be fabricated separately, joined, and further modified as appropriate. For example, when fabricated as distinct layers, microfluidic components may be bonded, generally face-to-face. These separate components may be surface-treated, for example, with reactive chemicals to modify surface chemistry, with particle binding agents, with reagents to facilitate analysis, and/or so on. Such surface-treatment may be localized to discrete portions of the surface. . .

DETD [0134] Exemplary methods for fabricating microfluidic systems are described in more detail in the patent applications identified above under Cross-References, which are incorporated herein by reference.

DETD [0137] Microfluidic systems may include any suitable structure(s) for the integrated manipulation of small volumes of fluid, including moving and/or storing fluid,. . .

DETD . . . suitable path, channel, or duct through, over, or along which materials (e.g., fluid, particles, and/or reagents) may pass in a microfluidic system. Collectively, a set of fluidically communicating passages, generally in the form of channels, may be referred to as a microfluidic network. In some cases, passages may be described as having surfaces that form a floor, a roof, and walls. Passages. . .

DETD [0141] Passages may branch, join, and/or dead-end to form any suitable microfluidic network. Accordingly, passages may function in particle positioning, sorting, retention, treatment, detection, propagation, storage, mixing, and/or release, among others.

DETD . . . and/or output reservoirs. Input reservoirs may store materials (e.g., fluid, particles, and/or reagents) prior to inputting the materials to a microfluidic network(s) portion of a chip. By contrast, intermediate reservoirs may store materials during and/or between processing operations. Finally, output reservoirs. . .

DETD [0151] Microfluidic systems may be used to manipulate and/or analyze particles. A particle generally comprises any object that is small enough to be inputted and manipulated within a microfluidic network in association with fluid, but that is large enough to be distinguishable from the fluid. Particles, as used here,. . .

DETD [0155] Cells used as particles in microfluidic systems may have any suitable origin, genetic background, state of health, state of fixation, membrane permeability, pretreatment, and/or population purity,. . . have intact membranes, and/or permeabilized/disrupted membranes to allow uptake of ions, labels, dyes, ligands, etc., or to allow release of cell contents. Cells may have been pretreated before introduction into a microfluidic system by any suitable processing steps. Such processing steps may include modulator treatment, transfection (including infection, injection, particle bombardment, lipofection,. . . or labels, and/or so on. Furthermore, cells may be

a monoculture, generally derived as a clonal population from a single cell or a small set of very similar cells; may be presorted by any suitable mechanism such as affinity binding, FACS, drug selection, etc.; and/or may be a mixed or heterogeneous population of distinct cell types.

DETD [0167] Viruses may be manipulated and/or analyzed as particles in microfluidic systems. Viruses generally comprise any microscopic/submicroscopic parasites of cells (animals, plants, fungi, protists, and/or bacteria) that include a protein and/or. . .

DETD [0169] Organelles may be manipulated and/or analyzed in microfluidic systems. Organelles generally comprise any particulate component of a cell. For example, organelles may include nuclei, Golgi apparatus, lysosomes, endosomes,. . .

DETD . . . mixtures, phages, viruses, and/or cells, among others. For example, the beads may be associated with a member of a specific binding pair (see Section VI), such as a receptor, a ligand, a nucleic acid, a member of a compound library, and/or. . .

DETD [0177] Microfluidic systems may include one or more input mechanisms that interface with the microfluidic network(s). An input mechanism generally comprises any suitable mechanism for inputting material(s) (e.g., particles, fluid, and/or reagents) to a microfluidic network of a microfluidic chip, including selective (that is, component-by-component) and/or bulk mechanisms.

DETD [0179] The input mechanism may receive material from internal sources, that is, reservoirs that are included in a microfluidic chip, and/or external sources, that is, reservoirs that are separate from, or external to, the chip.

DETD [0186] Microfluidic systems may include one or more positioning mechanisms. A positioning mechanism generally comprises any mechanism for placing particles at preselected. . .

DETD . . . particle position longitudinally and/or transversely. The term "longitudinal position" denotes position parallel to or along the long axis of a microfluidic channel and/or a fluid flow stream within the channel. In contrast, the term "transverse position" denotes position orthogonal to the. . .

DETD . . . mechanisms generally comprise any mechanisms in which a force acts directly on a particle(s) to position the particle(s) within a microfluidic network. Direct positioning mechanisms may be based on any suitable mechanism, including optical, electrical, magnetic, and/or gravity-based forces, among others.. . . particles. Suitable electrical mechanisms include "electrokinesis," that is, the application of voltage and/or current across some or all of a microfluidic network, which may, as mentioned above, move charged particles directly (e.g., via electrophoresis) and/or indirectly, through movement of ions in. . .

DETD . . . mechanisms in which a force acts indirectly on a particle(s), for example, via fluid, to move the particle(s) within a microfluidic network, longitudinally and/or transversely.

DETD [0199] Transverse positioning of particles and/or reagents in a microfluidic system may be mediated at least in part by a laminar flow-based mechanism. Laminar flow-based mechanisms generally comprise any positioning. . . flow streams, preferably one, flowing away from the junction. Due to the laminar flow properties of flow streams on a microfluidic scale, the unifying site may maintain the relative distribution of inlet flow streams after they unify as laminar outlet flow. . .

DETD [0203] Transverse positioning of particles and/or reagents in a microfluidic system may be mediated at least in part by a stochastic (or portioned flow) positioning mechanism. Stochastic transverse positioning mechanisms. . .

DETD [0211] Microfluidic systems may include one or more retention mechanisms. A retention mechanism generally comprises any suitable

mechanism for retaining (or holding, capturing, or trapping) particles at preselected positions or regions of microfluidic networks, including single or plural mechanisms, operating in series and/or in parallel. Retention mechanisms may act to overcome the positioning. . .

DETD [0214] Retention mechanisms may be based at least partially on particle contact with any suitable physical barrier(s) disposed in a microfluidic network. Such particle-barrier contact generally restricts longitudinal particle movement along the direction of fluid flow, producing flow-assisted retention. Flow-assisted particle-barrier. . .

DETD [0218] Chemical interactions may be specific. Specific mechanisms may use specific binding pairs (SBPs), for example, with first and second SBP members disposed on particles and passage surfaces, respectively. Exemplary SBPs may. . . below in Table 1, with the designations of first and second being arbitrary. SBP members may be disposed locally within microfluidic networks before, during and/or after formation of the networks. For example, surfaces of a substrate and/or a fluid layer component. . . layer component are joined. Alternatively, or in addition, an SBP member may be locally associated with a portion of a microfluidic network after the network has been formed, for example, by local chemical reaction of the SBP member with the network (such as catalyzed by local illumination with light).

TABLE 1

Representative Specific Binding Pairs

First SBP Member	Second SBP Member
Antigen	antibody
Biotin	avidin or streptavidin
Carbohydrate	lectin or carbohydrate receptor
DNA	antisense DNA or DNA-binding protein
enzyme substrate or inhibitor	enzyme
Histidine	NTA (nitrilotriacetic acid)
IgG	protein A or protein G
RNA	antisense RNA

DETD . . . Chemical interactions also may be relatively nonspecific. Nonspecific interaction mechanisms may rely on local differences in the surface chemistry of microfluidic networks. Such local differences may be created before, during and/or after passage/microfluidic network formation, as described above. The local differences may result from localized chemical reactions, for example, to create hydrophobic or hydrophilic regions, and/or localized binding of materials. The bound materials may include poly-L-lysine, poly-D-lysine, polyethylenimine, albumin, gelatin, collagen, laminin, fibronectin, entactin, vitronectin, fibrillin, elastin, heparin,. . .

DETD . . . force on the particles that is generally orthogonal to fluid flow. Such forces may be exerted by centrifugation of a microfluidic chip and/or by particle movement within a fluid flow path (see Example 9). Magnetic force-based retention mechanisms may retain particles using magnetic fields, generated external and/or internal to a microfluidic system. The magnetic field may interact with ferromagnetic and/or paramagnetic portions of particles. For example, beads may be formed at. . .

DETD . . . a blind-fill channel, where a channel has a inlet, but no outlet, either fixedly or transiently. For example, when the microfluidic device is made from a gas permeable

material, such as PDMS, gas present in a dead-end channel can escape, or be. . .

DETD . . . ion(s), polymer(s), material(s), complex(es), mixture(s), aggregate(s), and/or biological particle(s), among others, that contacts a particle or particle population in a microfluidic system. Reagents may play a role in particle analysis, including operating as chemical/biological modulators (interaction reagents), detection/assay reagents, solvents, buffers,. . .

DETD . . . modulators or biological modulators may include any reagent that is being tested for interaction with particles. Interaction generally includes specific binding to particles and/or any detectable genotypic and/or phenotypic effect on particles (or modulators). Further aspects of interactions and genotypic/phenotypic effects. . .

DETD [0240] Particles in microfluidic systems may be exposed to physical modulators/conditions using non-fluid-mediated mechanisms. However, these "non-fluid-mediated" mechanisms may use properties of fluid to. . . particles via fluid. The physical modulators/conditions may be applied to particles from sources that are external and/or internal to the microfluidic systems. Exemplary physical modulators/conditions may include thermal energy (heat), radiation (light), radiation (particle), an electric field, a magnetic field, pressure. . .

DETD [0246] Particles manipulated by a microfluidic system may be analyzed by one or more measurement mechanisms at one or more measurement sites. The measurement mechanisms generally. . .

DETD . . . particle (or a component or derivative thereof) and its neighbors (e.g., other particles), the solvent (including any matrix), and/or the microfluidic system, among others, and may be used to characterize molecular size and/or shape, or to separate a sample into its. . .

DETD . . . mechanism may be used to detect particles and/or particle characteristics at any suitable detection site, internal and/or external to the microfluidic system. 1

DETD [0256] Suitable internal detection sites may include any site(s) in or on a microfluidic system (a chip). These sites may include channels, chambers, and/or traps, and portions thereof. Particles or particle characteristics may be. . .

DETD [0257] Suitable external detection sites may include any site(s) away from or independent of a microfluidic system. External detection sites may be used to detect a particle or particle characteristic after removal of particles (or particle components) from a microfluidic system. These external sites may be used instead of and/or in addition to internal sites, allowing particles (or particle components). . . detected. These further manipulations and/or detection methods may overlap with, but preferably complement, the manipulations and/or methods performed in the microfluidic system, including mass spectrometry, electrophoresis, centrifugation, PCR, introduction into an organism, use in clinical treatment, and/or cell culture, among others.

DETD . . . localization, structure/modification, conformation, morphology, activity, number, and/or movement of DNA, RNA, protein, enzyme, lipid, carbohydrate, ions, metabolites, organelles, added reagent (binding), and/or complexes thereof, among others. The detected characteristics also may include cellular characteristics, such as any suitable cellular genotype or phenotype, including morphology, growth, apoptosis, necrosis, lysis, alive/dead, position in the cell cycle, activity of a signaling pathway, differentiation, transcriptional activity, substrate attachment, cell-cell interaction, translational activity, replication activity, transformation, heat shock response, motility, spreading, membrane integrity, and/or neurite outgrowth, among others.

DETD [0263] A microfluidic system may include any suitable number of particle release mechanisms. A release mechanism generally comprises any mechanism(s) for allowing a. . .

DETD [0274] Microfluidic systems may include one or more output mechanisms that interface with the microfluidic network(s). An output mechanism generally comprises any suitable mechanism for outputting material(s) (e.g., fluid, particles, and/or reagents) from a microfluidic system, or portions thereof, including selective and/or bulk mechanisms. The output mechanism may direct outputted material to any suitable location,. . .

DETD [0277] Cells may be cultured using a cell culture mechanism in microfluidic systems. The cell culture mechanism generally comprises any suitable mechanism for growing cells, including maintenance and/or propagation. Suitable cells are. . .

DETD [0279] A cell culture mechanism of a microfluidic system may include one or more culture chambers in which to culture cells. Culture chambers may have any suitable size, shape, composition, and/or relationship to other aspects of microfluidic systems, based on the number of cells to be cultured, size of cells, assays to performed on the cells, and/or growth characteristics of the cells, among others. The size of a culture chamber may be only large enough to hold one cell, several cells or more (2 to 50), or many cells (50 to 1000 or more) of a given cell size. Accordingly, culture chambers may be defined by a selected portion of a passage, an entire passage, or a set of. . . interest to enter the chamber. This height may be greater than, less than, and/or equal to other portions of the microfluidic network. Some or all of the surfaces of a culture chamber, such as the walls, roof, and/or substrate, may be treated or modified to facilitate aspects of cell culture, particularly specific or nonspecific cell attachment, cell survival, cell growth, and/or cell differentiation (or lack thereof), among others. Suitable methods of passage treatment and treatment agents are described above in Section VI,. . .

DETD . . . temperature, rate and frequency of media exchange, and/or the like. Environmental control mechanisms may operate internal and/or external to a microfluidic system. Internal mechanisms may include on-board heaters, gas conduits, and/or media reservoirs. External mechanisms may include an atmosphere- and/or temperature-controlled. . .

DETD [0285] Microfluidic systems are used for particle manipulations. Particle manipulations generally comprise any suitable sequence of unitary operations, for performing a desired. . .

DETD [0287] FIG. 1 shows an exemplary method 100 for microfluidic manipulation and analysis of particles with systems of the invention. Each step of method 100 may be repeated any suitable. . .

DETD [0288] Particles typically are initially inputted in an input step, shown at 101. Particle input introduces particles to a microfluidic system and may be mediated by any of the input mechanisms described above in Section IV.

DETD . . . release step, shown at 109, if particles have been retained. Suitable release mechanisms are described above in Section IX. Alternatively, microfluidic systems may be discarded before particle release, additional positioning, and/or output.

DETD . . . measured. Therefore, method 100 enables any suitable sequence of particle manipulations and analyses at one or plural positions within a microfluidic system.

DETD [0294] A basic manipulation of microfluidic analyses is IP. This sequence of steps may lead to output (IPO) or to (path 104), resulting in the basic. . .

DETD [0297] The microfluidic systems of the invention may be used for any suitable cell assays or methods, including any combinations of

cells, cell. . .

DETD [0298] The cell assays may characterize cells, either with or without addition of a modulator. Cell assays may measure cell genotypes, phenotypes, and/or interactions with modulators. These assays may characterize individual cells and/or cell populations/groups of any suitable size. Cells may be characterized in the absence of an added modulator to define one or more characteristics of the cells themselves. Alternatively, or in addition, cell may be characterized in the presence of an added modulator to measure interaction(s) between the cells and the modulator. Moreover,. . .

DETD [0302] Genotypic assays may be conducted on cells in microfluidic systems to measure the genetic constitution of cells. The genotypic assays may be conducted on any suitable cell or cell populations, for example, patient samples, prenatal samples (such as embryonic, fetal, chorionic villi, etc.), experimentally manipulated cells (such as transgenic. . . Nucleic acid hybridization with nucleic acids may be carried out with a dye-labeled probe, a probe labeled with a specific binding pair (see Section VI), a stem-loop probe carrying an energy transfer pair (such as a "molecular beacon"), and/or with a. . . aspects may include total DNA content (for example 2N, 4N, 8N, etc., to measure diploid, tetraploid, or polyploid genotypes and/or cell cycle distribution), number or position of specific chromosomes, and/or position of specific genes (such as adjacent the nuclear membrane, another. . .

DETD [0304] Phenotypic assays may be conducted to characterize cells in microfluidic systems, based on genetic makeup and/or environmental influences, such as presence of modulators. These assays may measure any molecular or. . .

DETD [0305] Aspects of a whole cell or whole cell population may include number, size, density, shape, differentiation state, spreading, motility, translational activity, transcriptional activity, mitotic activity, replicational activity, transformation, status of one or more. . . processes, intact/lysed, live/dead, frequency/extent of apoptosis or necrosis, presence/absence/efficiency of attachment to a substrate (or to a passage), growth rate, cell cycle distribution, ability to repair DNA, response to heat shock, nature and/or frequency of cell-cell contacts, etc.

DETD [0306] Aspects of cell organelles may include number, size, shape, distribution, activity, etc. of a cell's (or cell population's) nuclei, cell-surface membrane, lysosomes, mitochondria, Golgi apparatus, endoplasmic reticulum, peroxisomes, nuclear membrane, endosomes, secretory granules, cytoskeleton, axons, and/or neurites, among others.

DETD [0307] Aspects of cell constituents/components may include presence/absence or level, localization, movement, activity, modification, structure, etc. of any nucleic acid(s), polypeptide(s), carbohydrate(s), lipid(s), ion(s),. . . molecule, hormone, metabolite, and/or a complex(es) thereof, among others. Presence/absence or level may be measured relative to other cells or cell populations, for example, with and without modulator. Localization may be relative to the whole cell or individual cell organelles or components. For example, localization may be cytoplasmic, nuclear, membrane-associated, cell-surface-associated, extracellular, mitochondrial, endosomal, lysosomal, peroxisomal, and/or so on. Exemplary cytoplasmic/nuclear localization may include transcription factors that translocate between these two. . . include intracellular trafficking, such as protein targeting to specific organelles, endocytosis, exocytosis, recycling, etc. Exemplary movements may include endocytosis of cell-surface receptors or

associated proteins (such as GPCRs, receptor tyrosine kinases, arrestin, and/or the like), either constitutively or in response to ligand binding. Activity may include functional or optical activity, such as enzyme activity, fluorescence, and/or the like, for example, mediated by kinases,. . . structure (such as association with partners in, on, or about cells). Methods for measuring modifications and/or structure may include specific binding agents (such as antibodies, etc.), in vivo or in vitro incorporation of labeled reagents, energy transfer measurements (such as FRET),. . .

DETD . . . are expressed from reporter genes), and/or the like. Methods for measuring polypeptides may include enzymatic assays and/or use of specific binding members (such as antibodies, lectins, etc.), among others. Specific binding members are described in Section VI.

DETD [0312] Interaction generally comprises any specific binding of a modulator to a cell or population of cells, or any detectable change in a cell characteristic in response to the modulator. Specific binding is any binding that is predominantly to a given partner(s) that is in, on, or about the cell(s). Specific binding may have a binding coefficient with the given partner of about 10.sup.-3 M and lower, with preferred specific binding coefficients of about 10.sup.-4 M, 10.sup.-6 M, or 10.sup.-8 M and lower. Alternatively, interaction may be any change in a. . .

DETD . . . modulator may be labeled, such as with an optically detectable dye, and may be labeled secondarily after interaction with cells. Binding of the dye to the cell or cells thus may be quantified. Alternatively, or in addition, the cell may be treated or otherwise processed to enable measurement of a phenotypic characteristic produced by modulator contact, as detailed above. . .

DETD [0314] Cells and/or cell populations may be screened with libraries of modulators to identify interacting modulators and/or modulators with desired interaction capabilities, such as. . . effect (such as reporter gene response, change in expression level of a native gene/protein, electrophysiological effect, etc.) and/or coefficient of binding. A library generally comprises a set of two or more members (modulators) that share a common characteristic, such as structure. . .

DETD [0316] Microfluidic assays of cells and/or populations may measure activity of signal transduction pathways. The activity may be measured relative to an. . .

DETD [0317] Signal transduction pathways generally comprise any flow of information in a cell. In many cases, signal transduction pathways transfer extracellular information, in the form of a ligand(s) or other modulator(s), through the. . . an intracellular signal. The extracellular information may act, at least partially, by triggering events at or near the membrane by binding to a cell -surface receptor, such as a G Protein-Coupled Receptor (GPCR), a channel-coupled receptor, a receptor tyrosine kinase, a receptor serine/threonine kinase, and/or. . . so on, which may result, ultimately, in altered gene expression. In other cases, modulators pass through the membrane and directly bind to intracellular receptors, for example with nuclear receptors (such as steroid receptors (GR, ER, PR, MR, etc.), retinoid receptors, retinoid. . .

DETD . . . based at least partially, on the type of signal transduction pathway being assayed. Accordingly, signal transduction assays may measure ligand binding; receptor internalization; changes in membrane currents; association of receptor with another factor, such as arrestin, a small G-like protein such. . .

DETD . . . genotypic, phenotypic, and/or modulator interaction of cells and/or populations of cells. The cells and/or populations may be compared in distinct microfluidic systems or within the same

microfluidic system. Comparison in the same microfluidic system may be conducted in parallel using a side-by-side configuration, as exemplified by Example 3, in parallel at isolated sites,. . .

DETD [0322] Microfluidic systems may be used to perform single-cell assays, which generally comprise any assays that are preferably or necessarily performed on. . .

DETD [0324] Microfluidic systems may be used to sort or select single cells and/or cell populations. The sorted/selected cells or populations may be selected by stochastic mechanisms (see Example 2), size, density, magnetic properties, cell -surface properties (that is, ability to adhere to a substrate), growth and/or survival capabilities, and/or based on a measured characteristic of. . . specific phenotype, and/or the like). Cells and/or populations may be sorted more than once during manipulation and/or analysis in a microfluidic system. In particular, heterogeneous populations of cells, such as blood samples or clinical biopsies, partially transfected or differentiated cell populations, disaggregated tissues, natural samples, forensic samples, etc. may be sorted/selected. Additional aspects of cell sorting and suitable cells and cell populations are described above in Section III and below in Examples 9, 15, 23, and 26.

DETD [0326] Microfluidic systems may perform storage and/or maintenance functions for cells. Accordingly, cells may be introduced into microfluidic systems and cultured for prolonged periods of time, such as longer than one week, one month, three months, and/or one year. Using microfluidic systems for storage and/or maintenance of cells may consume smaller amounts of media and space, and may maintain cells in a more viable state than other storage/maintenance methods. Additional aspects of storing and maintaining cells in microfluidic systems are included in Section XI above and Example 10 below.

DETD [0328] Microfluidic systems may be used for any suitable virally based, organelle-based, bead-based, and/or vesicle-based assays and/or methods. These assays may measure binding (or effects) of modulators (compounds, mixtures, polymers, biomolecules, cells, etc.) to one or more materials (compounds, polymers, mixtures, cells, etc.). . .

DETD [0331] The following examples describe selected aspects and embodiments of the invention, including methods of fabricating, integrating, and using microfluidic systems, and devices, and mechanisms for manipulation and analysis of particles. These examples are included for illustration and are not. . .

DETD [0334] This example describes microfluidic systems for positioning and/or retaining single particles or groups of particles, based, at least in part, on divergent flow paths;. . .

DETD . . . particles may be analyzed by any suitable method, including optical and electrical methods, among others. The described mechanisms use a microfluidic flow path that diverges to form a quasi-stagnant fluidic region at the position of divergence. Particles entering this quasi-stagnant fluidic region from a microfluidic stream experience a reduction in velocity, which may be exploited to effect their "soft landing" in a suitable retention structure. . .

DETD [0340] FIG. 2A shows a system 110 for microfluidic manipulation and/or analysis of particles, in accordance with aspects of the invention. System 10 includes (1) an input reservoir 112, (2) a microfluidic network 114 having three fluidic channels 116, 118, 120, and (3) two output or waste reservoirs 122, 124. Particles are. . .

DETD [0345] FIG. 2B shows another system 110' for microfluidic manipulation and/or analysis of particles, in accordance with aspects of the invention. The operational principles for system 110' of FIG.. . .

DETD [0347] FIG. 3 shows yet another system 170 for microfluidic

manipulation and/or analysis of particles, in accordance with aspects of the invention. System 170 includes (1) a fluidic network 172. . .

DETD . . . this embodiment, gap 212 is slightly wider than the diameter of cells 206, so that it will accept only one cell. In other embodiments, and/or for other cells, gap 212 may be wide enough to accept two or more cells. Whatever the width of gap 212, wall 190 and partitions 192, 194, form a retention site 214 at which cell 204 or cells may be stably retained. Once cell 204 is positioned at the retention site by trap 180, its presence may tend to block or diminish fluid flow. . . draw additional cells between partitions 192, 194. As a result, in some embodiments, trap 180 may preferentially retain only one cell automatically, without any need for optical monitoring during positioning and/or retention. Thus, retention site 214 may be dimensioned based on the size of cells to be retained. For example, eukaryotic cells typically are about 2 to 10 μm in diameter, so gap. . .

DETD Microfluidic Systems for Trapping and Perfusing Particles

DETD [0350] This example describes microfluidic systems that position and retain single particles or sets of particles, and allow rapid, precise perfusion of the retained particles. . .

DETD . . . a range of cell phenotypes or responses when the population is homogeneous or clonal. Therefore, studies of cells in a microfluidic environment would benefit from microfluidic systems that automatically position and/or retain a set of cells at a preselected site on a microfluidic chip. Furthermore, these studies would benefit from mechanisms that allow the retained set of cells to be perfused with selected. . .

DETD [0354] This example describes microfluidic systems that enable a user to trap multiple cells within a cell retention chamber, and perfuse the trapped cells with. . .

DETD [0356] FIGS. 5-11 show a system 250 for microfluidic analysis of cell populations. This system is described in detail below, including (a) system description, (b) system production, (c) system. . .

DETD [0358] FIG. 5 shows a portion of a system 250 for microfluidic analysis of cell populations. System 250 includes a microfluidic layer 252 and a control layer 254. Microfluidic layer 252 forms a microfluidic network 256 of interconnected channels, depicted in blue and orange. Control layer 254 is positioned over, and abutting, the microfluidic layer, and includes valves and pumps (see also FIG. 8), depicted in purple. Exemplary dimensions presented below for system 250. . .

DETD [0359] The microfluidic layer includes microfluidic channels with distinct geometries and functions. Blue, flow channels 258 have a semi-circular or arcuate cross-sectional profile and are positioned. . . particle. Thus, these cell channels are used to position cells to preselected laminar flow streams and preselected regions of the microfluidic network. Perfusion channels 262, described more fully below, also are shown in orange and function to controllably perfuse retained cells.. . .

DETD . . . of reagent exposure to measure rapid cell responses may be conducted reproducibly with the rapid response times afforded by this microfluidic system.

DETD [0367] FIG. 8 shows additional aspects of microfluidic system 250. These additional aspects include macrofluidic reservoirs, and valves and/or pumps of the control layer that control fluid flow within the microfluidic network.

DETD . . . the macroscopic world. Each reservoir or well functions as a fluidic inlet or outlet connected directly to at least one microfluidic channel. Fluidic inlet-well A, shown at 330, provides for particle input, generally as a cell suspension. Fluidic inlet-well B, shown. . .

DETD . . . 250 may be formed using any suitable method. In an exemplary

approach, the system is formed by layering and fusing microfluidic layer 252, control layer 254, and a substrate layer, formed, for example, by a cover slip (not shown). Specifically, in this approach, the microfluidic and control layers are molded by soft lithography and then fused. Next, the resulting fused multilayer structure is bonded to the cover slip substrate layer. Finally, microfluidic channels are wetted with deionized water.

DETD [0385] The microfluidic system demonstrated here can be used for any suitable assay, such as screening compounds against a small population of cells, with the size of the small population be selected to be statistically representative of cell behavior. The particles may include cells and/or beads, among others. The cells may be nonadherent and/or adherent cells, either in suspension or attached to a substrate provided by the microfluidic system. The beads similarly may be nonadherent or adherent, and may be used to carry samples, reagents, and/or cells, among. . .

DETD [0389] Communication passages 402 may be size-selective channels configured to prevent movement of retained particles, generally cells, between each subsystem 250. However, passages 402 are configured to. . . to, from, and/or between retained cells. Furthermore, perfusion mechanisms 268 may be used to determine the effect of reagents on cell-cell communication mediated by passages 402.

DETD [0392] FIG. 11C shows a retention mechanism 410 that may be used in system 250 or any other suitable microfluidic system to form a positioned, two-dimensional array of retained particles. Mechanism 410 includes an array of individual traps 412 oriented. . .

DETD Microfluidic Systems for Parallel Retention and/or Treatment of

DETD [0394] This example describes microfluidic mechanisms and systems that position a plurality of particles and/or reagents at discrete transverse regions and flow paths within a. . .

DETD . . . may need to be averaged over many experiments to achieve meaningful results. Therefore, it would be desirable to have a microfluidic system that positions, treats, and analyzes particles or groups of particles adjacent one another at a microscopic level, to allow. . .

DETD [0398] The microfluidic systems described in this example position a plurality of particles or (particle populations) and/or reagents along distinct, transversely disposed flow. . .

DETD [0401] The microfluidic systems of this example may allow more efficient and meaningful use of microfluidic space for comparative analysis of particles and/or reagents.

DETD [0404] FIGS. 12 and 13 show a microfluidic system 420 (Embodiment 1) for retaining separate populations of particles, and exposing the populations to one or more selected reagents.

DETD [0430] System 480 was tested as described below. Microfluidic chips were fabricated according to system 480 of FIG. 13A and used for analysis of flow patterns and particle treatment. . .

DETD [0435] FIG. 13L shows a portion of microfluidic system 1820 that may be used to separately address particles and/or reagents to sets of particle traps. System 1820 includes. . . alternative embodiments, traps 1826 are disposed in a transverse channel, such as channel 1798 or a chamber, such as a cell chamber with size -selective channel around its perimeter.

DETD Microfluidic System for Multiplexed Analysis of Particles in an Array

DETD [0436] This example describes a microfluidic system that loads particles in a serially distributed set of particle retention sites, and separately addresses reagents to each of. . .

DETD . . . treating the cells in such microtiter plates, and measuring short-term consequences of such treatments, poses substantial technical

hurdles. Therefore, a microfluidic system is needed that forms more reproducible arrays of individual cells or small groups of cells at distinct positions, and. . .

DETD [0440] This example describes a microfluidic system that serially traps small sets of particles at preselected positions within the system, allowing treatment of the trapped particles. . . of traps. Thus, this design may be used to integrate a large number of traps into a single system. This microfluidic system also reduces the number of control lines required, as single control lines regulate sets of fluidic channels, such as. . . loading, but then fluidically isolated during particle treatment and measurement. This arrangement of the traps enables the fabrication of larger microfluidic systems that may be suitable for use in high-throughput drug discovery. For example, system 510 has a footprint of 2. . .

DETD [0441] FIG. 14 shows a microfluidic system 510 for forming and analyzing an array of particles. System 510 may be formed by any suitable technique, such as multilayer soft lithography, to include at least two distinct layers: (1) a microfluidic network layer 512, shown in blue and orange, and (2) a control layer 514, shown in pink. Channels having distinct. . .

DETD [0442] Microfluidic layer 512 includes two orthogonally directed networks. Particle loading network 516 is used to input and position particles, so that. . .

DETD Microfluidic Device for Forming and Analyzing a Particle Array Using a "Cell Comb"

DETD [0454] This example describes a microfluidic device for forming and analyzing arrays of small number of particles, such as cells; see FIGS. 17-20.

DETD [0456] In many applications, it is necessary to form an array of cell-analysis chambers, with each chamber containing the same number of cells. These chambers allow multiple experiments, such as drug screens, to be conducted in parallel, in a consistent and comparable fashion. Currently, standard analyses use wells of microtiter plates as cell chambers, distributing an equal volume of a cell suspension to each of the wells. The size of these chambers and thus the number of cells analyzed has been decreasing in response to efforts to reduce the. . . lead to huge errors in the detected reaction signals. Accordingly, with even fewer cells per well, for example, with single cell assays or when cells of interest are in limited supply, microtiter plates do not provide an adequate cell-analysis chamber unless cells are counted to place an equal number per well. Even then, microtiter plates are deficient for performing. . . drug are difficult to measure with microtiter plates, because adding and mixing steps cannot be performed very rapidly. Therefore, many cell-analyses would benefit from systems for efficiently loading, rapidly treating, and analyzing small numbers of cells.

DETD [0458] FIG. 17 shows a microfluidic device 610 for forming an array of single particles or small groups of particles. Device 610 includes an input channel 612,. . .

DETD . . . all chambers 618. Alternatively, filter 622 may be formed by smaller, "leak" channels within filter channel 616, or by posts, obstacles, or protrusions that extend into a portion of filter channel 616, or that are disposed adjoining or adjacent an end of the filter channel. The diameter of the smaller channels, or the spacing of the posts/obstacles, determines the size of particle retained in chamber 618. Thus, as long as the diameters of these smaller channels, or the maximum spacing between these posts/obstacles , are sufficiently less than the diameter of a particle to be retained, the particle will be confined to chamber 618. . .

DETD . . . receive a fixed number of input particles 620, such as a single

particle. Such input particles may have a common size, such as cells from a homogeneous cell population, or they may have a range of sizes, such as cells from blood. In some embodiments, the diameter of filter channel 616 allows size-selective retention of a single particle. For example, the diameter may be large enough to receive certain particles in a heterogeneous particle population, such as red blood cells, but small enough to exclude others, such as white blood cells. Filter 622 also acts size selectively, as described above, so in combination with chamber 618, individual filter channels 616 may be designed to retain a single cell within a defined size range.

Alternatively, individual filter channels may be designed to retain a group of two or more cells, with each cell having a minimum size that is retained by filter 622.

DETD [0468] Cell combs, described in this example, may be useful in a variety of applications. For example, cell combs may be useful in drug discovery, serving as replacements for microtiter plates in cell assays to provide tighter control of the cell numbers. With current technology, the fabrication of each cell chamber in a cell comb device can be carried out with precision. Therefore, cell assays may be performed with an array of cells formed using this device, with reduced signal variation from chamber to chamber, even with single-cell assays.

Cell combs may, more generally, be used with a variety of micron-sized particles, in addition to cells, such as fluorescently or enzymatically coated beads. This device also can operate in gas phase, as long as the size of the particles of interest is larger than the pore size of the filter units. Cell combs also can be cascaded so that objects of different sizes are filtered out at different stages.

DETD [0471] One goal of microfluidic systems is the capability of retaining particles at preselected positions for subsequent treatment and analysis. Traps that perform such retention. . .

DETD . . . been dimensioned to trap a single particle; however, they alternatively may be dimensioned to trap two or more particles. The microfluidic system with respect to which each retention mechanism is illustrated, particularly positioning mechanism 264 and perfusion mechanism 268, is described. . . the positioning and perfusion mechanisms. However, the retention mechanisms presented in this example may be combined with any other suitable microfluidic mechanisms for particle analysis.

DETD [0475] FIG. 21 shows a microfluidic system 710 for positioning, retaining, and/or perfusing a single particle, in accordance with aspects of the invention. Portions of system. . .

DETD [0477] FIG. 22 shows another microfluidic system 740 for positioning, retaining, and/or perfusing a single particle, in accordance with aspects of the invention. View 742 shows a color-coded schematic of a system 740, whereas view 744 shows a photograph of an actual microfluidic system formed according to view 742, but flipped horizontally. System 740 includes a trap 746 positioned centrally at T-junction 714.. . .

DETD [0479] FIG. 23 shows yet another microfluidic system 790 for positioning, retaining, and/or perfusing a single particle, in accordance with aspects of the invention. System 790 includes. . . 730 by about 5 μm. View 802 shows a line representation of trap 792, but includes a portion 804 of microfluidic system outside of distal wall 716. Sectional views 806, 808 show how retention blocks 800 extend outward and downward from. . .

DETD . . . focus. In view 816, the focal plane is near the substrate surface, showing sharp lines at corners 820, where the microfluidic layer 822 contacts substrate 730. The bottom perimeter 824 of blocks 800 is blurry because bottom surface 814 is

raised. . .

DETD Mechanisms for Reusable Microfluidic Systems

DETD [0481] This example describes mechanisms that promote reuse of microfluidic systems, including mechanisms for release, collection, and/or resuspension of particles; see FIGS. 24-28.

DETD [0483] Microfluidic systems often are designed for single use. Such single-use systems may be used to retain and analyze a single cell. . . macroscopic volumes of cells and reagents, and is time consuming for initialization. Thus, there is a need for a reusable microfluidic system that releases retained particles after their analysis, freeing the system (or cells) for additional analysis.

DETD [0485] This example describes microfluidic mechanisms that enable formation of reusable microfluidic systems. These microfluidic mechanisms include (1) a particle release mechanism, (2) a particle collection mechanism, and (3) a particle suspension mechanism. The particle. . . well over time. These three mechanisms alone, or in any suitable combination, may enable more efficient and economical use of microfluidic systems for particle analysis.

DETD [0487] FIG. 24 shows a microfluidic system 850 having a particle release mechanism 852 and a particle collection mechanism 854, in accordance with aspects of the. . .

DETD [0491] Fluid flow through size-selective channel 872, and thus particle release, is controlled by valve V2 (see FIG. 24). Valve V2 is a control-layer valve disposed over reservoir channel 870. When valve V2 is closed, reservoir channel is compressed, forcing fluid outward through size-selective channel 872 into trap 858. This releases trapped particles, propelling them out of trap 858 into a flow stream, such. . . are closed, and the shield buffer is running. Thus, the main flow stream goes from the buffer wells to the cell culture area, described below. When valve V2 is opened, reservoir channel 870 expands, bringing fluid in through size-selective channel 868 and refilling the reservoir channel.

DETD . . . during release. Fluid flows through retention area 906 to outlet 910 by passing through filter channels 908, which act as size-selective channels that prevent released particles from flowing to the outlet. Thus, released particle are collected in retention area 906. When the collected particles are cells, the retention area may be used to culture cells to promote cell growth, differentiation, and/or response to a treatment, such as by perfusion mechanism 860. Alternatively, the retention area may be operatively. . .

DETD [0499] Standard particle input mechanisms, such as inlet-well 330 of FIG. 8, are sufficient for single-use microfluidic systems. However, these mechanisms may be inadequate for reusable systems. In reusable systems, it may be desirable to load a. . .

DETD [0500] FIG. 28 shows a particle suspension mechanism 920 that may be integrated into reusable microfluidic systems, such as systems 850 and 880 described above. This suspension mechanism helps to maintain particles in suspension and/or helps to resuspend settled particles during the course of analyses with a reusable microfluidic system. Mechanism 920 includes an inlet reservoir 922, recirculation channels 924, and pumping valves 926. Inlet reservoir 922 receives and. . .

DETD Microfluidic Mechanisms for Adjustable Reagent Delivery

DETD . . . volumes of the reagent are dispensed to provide a range of doses. However, this approach may not be suitable with microfluidic systems, because it may not be practical to dispense metered volumes in a microfluidic system and because it may require a mixer to mix and thus dilute such a dispensed volume. Thus, there is a need for a microfluidic mechanism that dispenses a premixed reagent at a range of selected concentrations,

using a small number of reagent stocks.

DETD . . . and second reagents at a range of concentrations, in accordance with aspects of the invention. Dilution mechanism 960 includes a microfluidic layer 962 having first and second reagent reservoirs 964, 966, and first and second controllable flow channels 968, 970 acting. . .

DETD [0512] The dilution mechanisms described above may be used as part(s) of any suitable microfluidic device, for any suitable applications. For example, dilution mechanism 990 may be used in microfluidic system 250 in FIG. 8 of Example 2 to prepare and deliver a desired mixture of reagents for particle perfusion,. . .

DETD Microfluidic Sorting Mechanisms Based on Centrifugal Forces

DETD [0515] Microfluidic analyses of particles may benefit from or even require sorting crude or heterogeneous input populations of particles into their components.. . . constantly monitored and actively directed to distinct sorting bins based on optical properties. Thus, there is a need for a microfluidic sorting mechanism that separates distinct particles, potentially passively, based on different physical properties of the distinct particles.

DETD . . . liquid columns having different heights in input and output reservoirs. However, these sorting mechanisms may be integrated into any suitable microfluidic system.

DETD [0519] FIGS. 31 and 32 show a microfluidic system 1020 having a sorting mechanism 1022 that separates particles according to physical differences between the particles, in accordance with. . . may be formed with any suitable dimensions. Furthermore, mechanism 1022 may sort particles from any suitable source, such as a microfluidic treatment or analysis, into any desired number of outlet channels and/or other microfluidic mechanisms or structures, such as culture chambers, retention mechanisms, perfusion mechanisms, and/or the like.

DETD [0523] FIG. 33 shows a microfluidic system 1060 having a sorting mechanism 1062 with modified sorting parameters, in accordance with aspects of the invention. Sorting mechanism. . .

DETD [0525] FIGS. 34 and 35 show another microfluidic system 1080 having a sorting mechanism 1082 with modified sorting parameters, in accordance with aspects of the invention. Sorting mechanism. . .

DETD . . . described in this example. The particles are split into two streams 1100 in the separation region. The lower stream is enriched for cells (red), and the upper stream is enriched for beads (green). Flow of particles through the system is powered by a 1-cm high column of fluid in the. . .

DETD [0531] The systems shown in this example have the ability to passively enrich particles based on sorting mechanisms that distinguish physical properties of particles. The approximately two-fold enrichment obtained using these systems may be sufficient to facilitate or improve some microfluidic analyses. Furthermore, each of these systems may be modified and refined, and/or connected in series to improve enrichment of desired particles.

DETD Microfluidic Systems for Manipulating Sets of Particles

DETD [0532] This example describes microfluidic systems having relatively large chambers, in which larger sets of particles, such as adherent and/or nonadherent cells, can be retained,. . .

DETD [0534] The introduction and/or removal of particles into and out of microfluidic systems, at macroscopic/microscopic interfaces, may inefficient and/or harmful. For introduction, particles must be placed in suspension and often are introduced. . . example, by evaporation of inlet- or outlet-reservoir liquid. Accordingly, it is desirable to avoid repeatedly introducing and removing particles from microfluidic systems during a sequential set of assays. Therefore, there is a need for chambers for storing, treating, maintaining, measuring, and/or. . .

DETD [0537] This example describes various microfluidic systems

that address and solve some or all of the problems and issues cited above. These microfluidic systems may be formed using multilayer soft lithography, as described elsewhere in this Detailed Description and in the Cross-References. Channels. . . such molds may be used to form particle chambers of various dimensions. These channels and/or chambers may be integrated into microfluidic systems that include valves, pumps, rotary mixers, filters, sorters, multiplexers, perfusion mechanisms, and/or additional particle retention sites, among others, to. . .

DETD [0539] FIGS. 39-43 illustrate exemplary microfluidic networks 1130 that include relatively large chambers 1132 for retaining particles, in accordance with aspects of the invention. These networks. . . result, this process allows formation of chambers with width-to-height ratios less than about 10:1 that do not collapse. In contrast, microfluidic channels having width-to-height ratios greater than 10:1 formed by a standard soft lithography process may collapse more frequently.

DETD . . . posts may project downward from the roof of the channel to contact the substrate, generally being integrally formed in the microfluidic layer during fabrication of this layer. Alternatively, or in addition, these columns or posts may project upward from the substrate,. . .

DETD [0544] FIG. 45 shows a microfluidic system 1180 having a microfluidic network 1130 through which fluid flow is more flexibly controlled. Specifically, fluid flow through chamber 1132 is controllable by two. . .

DETD . . . then allows the detached cells to be flushed from the system, either to output reservoir 1136 or to any additional microfluidic mechanism or set of mechanisms, as described throughout this detailed description.

DETD [0547] FIG. 46 shows a microfluidic system 1210 with a cell chamber 1212 formed as a looped channel or ring structure, in accordance with aspects of. . .

DETD [0549] FIGS. 47-49 shows another microfluidic system 1240 with a chamber 1242 formed as a looped channel or ring structure, in accordance with aspects of the. . .

DETD [0557] FIG. 50A shows a system 1910 for depositing cells (or other particles) in a microfluidic chamber 1912, based on an asymmetrically disposed flow path. Particles and fluid flow into chamber 1912 from inlet channel 1914.. . .

DETD [0565] FIG. 50C shows a cell chamber 1970 that may be used to deposit (and retain) cells in one or two compartments 1972, 1974. Compartments 1972, 1974 may be connected by radially arrayed, size-selective channels 1976 to form a "spoked wheel" structure. Cells (or other particles) may be inputted from first input channel 1978 and deposited in compartment 1972. Fluid may flow through size -selective channels 1976 to second input channel 1980. Alternatively, or in addition, additional cells, such as a distinct cell type, may be inputted from second input channel 1980 to be deposited in outer compartment 1974, with fluid flowing toward first input channel 1978. With each of the two compartments occupied by distinct cell populations, cell-cell communication may be analyzed by passage of released cell components (or extended cell structures) through the size-selective channels between the two compartments. In alternative embodiments, the first and second compartments may have any suitable geometry, such as. . . increase the area of communication between the two compartments. Furthermore, additional compartments may be added to measure interactions between additional cell types.

DETD [0567] Cell chamber 1990 is a modified version of chamber 1970 that includes an overflow capability. Here, inner compartment 1972 acts as a chamber that is connected to overflow compartment 1992 by

transverse passages 1994, in addition to size-selective channels 1976. Accordingly, input channel 1978 may be used to direct most of inputted cells (or other particles) into inner. . .

DETD [0569] The microfluidic systems described here may be used for the manipulation of adherent and nonadherent cells. For example, after introduction to a. . .

DETD . . . concentration has been achieved, cells are loaded using a manual pipettor into the input well and cells flow into the microfluidic channel structures under the head flow generated by the column of liquid. Once adhered, adherent cells can be resuspended in the microfluidic channel by addition of trypsin-EDTA or other cell-detaching agents.

DETD [0571] The microfluidic layer and substrate may be treated (or left untreated) to promote cell flow, cell viability, cell adhesion or nonadhesion, cell. . .

DETD Systems for Electrophysiological Analysis of Cells in a Microfluidic Environment

DETD [0572] This example describes microfluidic systems for positioning, retaining, treating, and/or measuring cells, particularly for electrophysiological analyses; see FIGS. 51-58.

DETD . . . approach, a glass electrode with a diameter of about 0.1-1 μm is electrically sealed against the membrane of a single cell, surrounding a membrane "patch" on the cell. The patch then may be left intact, separated from the cell, "perforated" with channel-forming agents, or penetrated, based on the type of information desired. With both intact patches and patches separated from a cell, the size of the patch and the density of channels in the membrane determine the number of channels being analyzed. Thus, different. . . of channels in "macropatch recording." Alternatively, membrane patches can be perforated or penetrated to measure electrical properties of the entire cell membrane, in "whole-cell" patch-clamp studies. Perforated patches introduce a channel-forming agent, such as the antibiotics nystatin or amphotericin B, into the membrane. Perforated patches enable whole cell recording of channel activity with loss of larger cytoplasmic components. Penetrated patches place an electrode inside a cell, so that the electrode and the cell's cytoplasm are continuous. Accordingly, penetrated patches also enable whole-cell patch-clamp recording.

DETD [0578] This example describes microfluidic devices that allow measurements of ion channel activity. These devices position a single cell in abutment with an aperture, so. . .

DETD [0580] FIG. 51 shows a microfluidic device 1310 for measuring ion currents, in accordance with aspects of the invention. Device 1310 includes a planar patch clamp electrode. . .

DETD . . . elsewhere in this Detailed Description. The fluidic layer may be controlled by any suitable control mechanism, such as an overlying microfluidic control layer 1320. The base layer may be formed out of any suitable material, such as glass, plastic, and/or an. . .

DETD [0584] FIGS. 52-58 shows a microfluidic system 1340 for single-cell patch-clamp recordings, in accordance with aspects of the invention. System 1340 includes a fluid-layer network 1342. . .

DETD [0588] Cell positioning mechanism 1354 generally comprises any mechanism that acts to position single cells within microfluidic network 1342. In addition to simple flow channels, the cell-positioning mechanism may include a focusing mechanism 1360. Focusing mechanism 1360. . .

DETD [0589] Cell positioning mechanism 1354 stochastically segregates single cells using a divided-flow mechanism 1374, downstream from focusing mechanism 1360 or 1372; see. . . 1380, 1382 (labeled "W1" and "W2," respectively, in FIG. 54). These outlet channels include a narrowed portion 1384 and a size-restrictive channel 1386

that determine the relative flow rate through each corresponding outlet channel. Narrowed portion 1384 has a substantially larger diameter than size-selective channel 1386, so that most of the flowing fluid (and cells) passes through narrowed portion 1384. However, some fluid passes through size-restrictive channel 1386, eventually bringing a single cell 1388 to the mouth of the channel.

DETD [0590] Cell retention mechanism 1356 generally comprises any mechanism for retaining a cell at a desired position, generally adjacent an orifice and/or electrode(s). Here, the cell retention mechanism functions at the channel mouth; see FIGS. 54 and 57. In particular, cell 1388 cannot enter size-restrictive channel 1386 because the cell is too large. However, the pressure drop across size-restrictive channel 1386 pulls cell 1388 against the channel mouth, holding cell 1388 in position. Positioned cell 1388 may restrict or block flow through size-restrictive channel 1386, so that additional cells no longer are urged toward channel 1386. Cell 1388 also is positioned over an orifice 1390 (see FIG. 56) defined by the substrate layer. In alternative embodiments, single. . .

DETD [0595] Microfluidic system 1340 may be configured in many suitable ways. For example, reagent inlet channels may unite, entering chamber E1 through. . .

DETD Microfluidic System for Multiplexed Analysis of Cells by Patch Clamp

DETD [0596] This example describes microfluidic systems for performing electrophysiological analysis on one or more cells out of a set of single cells; see FIGS. 59-61.

DETD [0601] This example provides a multiplexed version of a single-aperture microfluidic device, with a defined number ("n") of individually controllable apertures. Each individually controllable aperture may be used to analyze a single. . .

DETD [0606] FIG. 60 shows a microfluidic device 1450 that is a multiplexed version of device 1430, in accordance with aspects of the invention. Device 1450 may include. . .

DETD [0608] Device 1450 may be modified in any suitable fashion, incorporating any suitable microfluidic mechanisms, such as those described in this Detailed Description. For example, device 1450 may be structured to load cells serially. . . described above in Examples 3-5. Furthermore, device 1450 may be included in an array of such devices to form a microfluidic array. Alternatively, or in addition, device 1450 may include a perfusion mechanism, such as that described in Examples 2 and. . .

DETD Multilayer Mold-Fabrication Method of Varying Height and/or Cross-Sectional Geometries of Molded Microfluidic Structures

DETD [0610] This example describes a method for producing, by soft lithography, microfluidic devices in which the cross-sectional geometry and/or height of structures within and/or between microfluidic networks vary; see FIGS. 62-71.

DETD [0612] A microfluidic network may include structures having a variety of functions. For example, regulatable channels may include deflectable valves, acting to partially. . . of the width of the channels, rather than just the central portion, as with arcuate channels. Other channels may be size-selective or particle-restrictive, preventing entry of particles greater than a given size. These particle-restrictive channels may have a height that is less than the diameter of particles of interest. Furthermore, microfluidic networks may include cell/culture chambers with roof heights that are greater than more narrow channels, as described in Example 10, to improve the functionality. . .

DETD . . . be heated to round their edges into an rounded/arcuate configuration. Accordingly, these remaining regions of the resulting

mold may produce microfluidic channels of complementary structure using soft lithography. In other embodiments, multiple layers of photoresist may be built up by sequential. . .

DETD [0614] Despite the importance of varying height and/or cross-sectional shape across a microfluidic network, molds formed from a single layer of selectively removable material, such as photoresist, may not allow sufficient flexibility in the structure of a microfluidic network formed from the mold. For example, the depth to which the single layer may be removed cannot be varied. . .

DETD . . . in this example may be used to form channels with different cross-sectional geometries and/or heights at distinct positions within a microfluidic network. A mold is fabricated using plural layers of photoresist that are each individually patterned, selectively removed according to the. . . pattern is the sum of the remaining portions from each of the plural layers. Using the mold to form a microfluidic network allows various types of channels or other passages to be formed. Channels with a rounded/arcuate cross-sectional shape may be. . . to promote particle movement and to enable precise delivery of one or more particles to a specific area of a microfluidic network. The specific area can be as small as the dimension of a single particle, such as a cell. These structures and other suitable microfluidic structures may be produced using the method described below. This method focuses on formation of a fluid layer, but may be suitable for any portion(s) of a microfluidic system, including a control layer or a base layer (see Example 11).

DETD . . . The fluid-layer mold may be used subsequently in a second series of steps, as described below, to mold a complementary microfluidic layer by soft lithography. FIGS. 62-68 illustrate how fluid-layer mold 1480 may be formed by sequentially disposing, patterning, and selectively. . .

DETD [0627] The fluid-layer and control-layer molds fabricated above may be used to mold a microfluidic chip using any suitable material, particularly an elastomeric material, such as polydimethylsiloxane (PDMS). Exemplary PDMS elastomers are General Electric Silicones. . .

DETD [0631] FIGS. 70 and 71 show photographic images of fluid-layer molds and the corresponding microfluidic chips formed with these molds. The microfluidic networks represented here, have been shown and described in system 1340 of Example 11 (FIG. 70) and in a modified. . .

DETD Detection System for Kinetic Analyses in Microfluidic Systems

DETD . . . detection system, including a modulation-demodulation method and the use of tracer materials, for analysis of kinetic reactions involving particles in microfluidic systems; see FIGS. 71A-F.

DETD [0634] Microfluidic systems may be used to measure the kinetics of many aspects of cellular metabolism. However, metabolic processes of physiological significance. . .

DETD . . . a result, some cellular processes that occur over relatively longer time periods may be more difficult to monitor in a microfluidic system due to this photobleaching.

DETD . . . source produces a reduced emission signal and signal-to-noise ratio, since the emission signal is proportional to the illumination intensity. Therefore, microfluidic analyses would benefit from a detection system that reduces photobleaching, increases the ratio of signal-to-noise, and/or allows kinetic analysis of. . .

DETD [0638] This example describes an exemplary detection system for use with microfluidic assays, in accordance with aspects of the invention. The detection system may include a modulation-demodulation mechanism; see FIGS. 71B-71E. This. . .

DETD . . . include a conventional microscope or other suitable optical device that is separate from, or partially or wholly integrated with, a microfluidic system.

DETD [0646] Exemplary Results using a Modulation-Demodulation Mechanism for

Microfluidic Analysis

DETD . . . a reagent-particle interaction occurs in a single experiment. Here, a biotinylated bead has been loaded into a trap on a microfluidic chip, such as a chip designed according to system 250 of Example 2. Dye-labeled streptavidin (reagent) is exposed to the. . .

DETD [0649] FIG. 71E shows the ability of an embodiment of the microfluidic detection system to measure a kinetic response of signal transduction in a cell. A calcium sensor dye, Fluo-3, was loaded into a cell, and the cell was trapped in a microfluidic chip, such as a chip designed according to system 250 of Example 2. The trapped cell was stimulated with ionomycin,. . .

DETD . . . not interfere optically or chemically with reagent dyes used to measure information about particles. Inert dyes may be nonbinding or binding. Nonbinding dyes do not bind to particles and may simply mark fluid volumes. Binding dyes may bind to particles, but do not contribute directly to a detected result from particles. By contrast, reactive dyes react with particles. . .

DETD [0654] FIG. 71F shows use of an embodiment of modulation-demodulation mechanism 2020 and a tracer dye in a microfluidic system to measure the rate at which reagent is exposed to particles. A perfusion mechanism, such as mechanism 268, was. . . maximum value in less than 100 milliseconds. Accordingly, rapid kinetic analyses on a millisecond time scale may be performed using microfluidic systems described herein.

DETD Microfluidic Analysis of a Heterogeneous Particle Population--Part I

DETD [0655] This example describes microfluidic systems for sorting and analyzing heterogeneous populations of particles, particularly cells, based on differences in particle size; see FIG. 72.

DETD [0656] Heterogeneous cell populations, such as blood, present a challenge for rapid analysis. Cells of interest in blood generally need to be separated. . . interest to avoid interference from these other cells. Accordingly, blood may need to be treated/manipulated to selectively lyse, coagulate, pellet, bind, and/or modify, among others, specific cells within the blood. Such manipulations add to the time and expense required for analysis. . . diagnostic procedures using whole blood are expensive and slow. Therefore, integrated systems are needed that automatically sort and analyze heterogeneous cell populations on a microfluidic scale.

DETD [0658] This example describes microfluidic systems that sorts blood cells and other heterogeneous particle populations according to diameters of individual particles. With these systems very. . .

DETD [0659] FIG. 72 shows a microfluidic system 1520 sorting cells. System 1520 is based on system 250 of Example 2 and includes positioning and retention mechanisms. . . A blood sample was introduced into system 1520 and directed toward retention chamber 270. Cells 1522 of this sample include red blood cells and platelets, but do not include detectable white blood cells, which would be retained by the retention mechanism due to. . . These white blood cells are too large to pass through channels 300. Therefore, system 1520 may be used to separate red blood cells and platelets from white blood cells, for selective analysis of the white blood cells (or red blood cells) in the system.

DETD Microfluidic Interaction of Specific Binding Pairs on Beads

DETD [0664] This example describes detection of interaction between a specific binding pair, biotin and avidin, on beads in a microfluidic system; see FIGS. 73-74.

DETD [0667] A specific binding pair, biotin/streptavidin, was selected for interaction on beads; see FIG. 73. Biotin is a vitamin with

a molecular weight of 244 daltons. Its partner, avidin, binds biotin with fierce tenacity, being the strongest non-covalent attachment known, with an association constant of 10.sup.15 M.sup.-1. This binding reaction has been studied intensively for many decades, and there is a rich literature. The great strength of this binding suggests that it might be a good model system for the study of biological binding reactions in general. It has also formed the basis for many detection and signal amplification strategies for both research and. . .

DETD . . . amphibia, and reptiles. The protein streptavidin, produced by the bacterium Streptomyces avidinii, has a structure very similar to avidin, also binding biotin tightly. However, streptavidin often exhibits lower nonspecific binding, and thus is frequently used in place of avidin.

DETD [0670] Materials for measuring biotin/avidin interaction were as follows. A microfluidic chip was fabricated based on system 250 of Example 2. Beads, 6.7-micron biotinylated polystyrene microspheres, were obtained from Spherotech Corporation.. . . BSA (sterile filtered), and the streptavidin conjugated fluorophores streptavidin-Alexa 350, streptavidin-Alexa 488, and streptavidin-PE (phycoerythryn), each obtained from Molecular Probes. Binding reactions were monitored with an inverted fluorescent microscope connected to a video camera.

DETD . . . these cases, the procedure was repeated without constant exposure to V, opening the UV shutter only long enough to document binding.

DETD . . . yield a detectable signal. However, more sensitive detection mechanisms, such as a laser scanning cytometer may allow detection of streptavidin-PE binding.

DETD Measuring Ion Flux in Cells Using a Microfluidic System

DETD [0681] This example describes analysis of intracellular ion concentrations, such as calcium ion concentrations, using a microfluidic system; see FIG. 75.

DETD [0685] Materials used for measuring intracellular calcium levels were as follows. A microfluidic chip was constructed based on a modified version of system 850 of Example 7. Fluo 3/AM, a fluorescent Ca.sup.+2 indicator. . .

DETD Microfluidic Analysis of Cell-Surface Markers

DETD . . . the CD8.sup.+ T lymphocytes and the target cells (Anderson et al., 1987; Eichmann et al., 1987; Gallagher et al., 1988). Binding of the CD8 antigen to class I MHC molecules enhances the activation of resting T lymphocytes. CD8 recognizes an antigen. . .

DETD [0708] Materials used for analysis of CD4 and CD8 were as follows. Microfluidic chips was constructed based on a modified version of system 850 of Example 7. Jurkat T-cells were cultured in RPMI.. . .

DETD [0713] The chip was prepared by running deionized water through the microfluidic network and then was mounted on an inverted fluorescent microscope. The 100+ or 63+ oil-immersion lens was used to maximize. . .

DETD [0725] Anti-CD8 antibody-conjugate did not bind to Jurkat cells, and therefore little or no red fluorescence was visible in the time frame needed to visualize the green fluorescence of the anti-CD4 antibody-conjugate. The procedure may be repeated with continuous UV exposure to observe antibody binding in real-time.

DETD Measuring Cell Lysis in a Microfluidic System

DETD [0750] Acridine orange (AO) was used for staining. AO binds to single stranded nucleic acids as a dimer, which fluoresces red in color, and to double stranded nucleic acids as. . . which fluoresces green. This difference in fluorescent wavelength is caused by differential accessibility of AO molecules to the nucleic acid binding sites. AO fluorescence is also pH sensitive, staining acidic organelles, such as lysosomes, orange.

DETD [0752] Materials used for measuring lysis were as follows. Microfluidic chips was constructed based on system 250 of Example 2. Jurkat T-cells were cultured in RPMI. Acridine Orange was dissolved. . .

DETD [0759] The chip was preparing by washing the microfluidic network with deionized water, and then was mounted on an inverted fluorescent microscope. The microscope's 63+ oil-immersion lens was used. . .

DETD Inducing and Detecting Cell Apoptosis in a Microfluidic Environment

DETD [0768] This example describes induction and detection of cell apoptosis in a microfluidic system; see FIG. 76.

DETD . . . can act as a marker for apoptosis. In normal viable cells, phosphatidylserine is located on the cytoplasmic side of the cell membrane. However, in apoptotic cells, PS is translocated from the inner to the outer leaflet of the plasma membrane, thus exposing PS to the cell exterior..sup.6 In leukocyte apoptosis, PS on the outer surface of the cell marks the cell for recognition and phagocytosis by macrophages..sup.7,8 The human anticoagulant, annexin V, is a 35-36 kD Ca.sup.+2-dependent phospholipid-binding protein that has a high affinity for PS..sup.9 Annexin V can identify apoptotic cells by binding to PS exposed on the outer leaflet..sup.10 Bound annexin V may be detected through a dye, a specific binding member conjugated to annexin V, an anti-annexin-V antibody, and/or the like.

DETD [0774] This example demonstrates induction and detection of cell apoptosis in a microfluidic system. Jurkat cells are positioned and retained in a microfluidic system, and then programmed cell death is initiated by exposure of these cells to hydrogen peroxide. Translocation of PS to. . .

DETD [0775] Materials used were as follows. Microfluidic chips were constructed based on system 250 of Example 2. Jurkat T-cells were cultured in RPMI. The VYBRANT Apoptosis Assay. . .

DETD [0781] Binding Buffer (BB) was loaded into the shield buffer well of the chip.

DETD Analysis of Aquatic Microorganisms in a Microfluidic System

DETD [0816] This example describes the capture and visualization of aquatic microorganisms, such as plankton, using a microfluidic system.

DETD [0820] This example provides a microfluidic system capable of manipulating and detecting small plankton, particularly picoplankton (0-2 μm), ultraplankton (2-5 μm), and/or nannoplankton (5-60 μm). Plankton may be retained, treated, and/or detected in an integrated microfluidic environment.

DETD [0821] Plankton were manipulated and detected in a microfluidic system as follows. A sample of seawater was collected from San Francisco Bay and centrifuged to concentrate organisms in the sample. A 20 μL aliquot of the concentrated sample was loaded into the input reservoir of microfluidic system 250, described in Example 2 above. Naturally-fluorescent plankton were retained in chamber 270 and detected successfully by fluorescent microscopy. . .

DETD . . . example, plankton may be collected from freshwater sources or cultured, an aqueous plankton sample may be loaded directly into a microfluidic environment without concentration, and/or retained plankton may be exposed to any suitable reagents. Alternatively, or in addition, microfluidic systems may be used that sort a heterogeneous population of plankton according to a physical property (such as size or density, among others) or a measured property/characteristic (such as labeling with a dye and/or specific binding member).

DETD Analysis of Membrane Trafficking in a Microfluidic System using Membrane Dyes

DETD [0823] This example describes microfluidic analysis of

membrane trafficking pathways in cells treated with membrane-labeling dyes.

DETD [0826] Some "FM" dyes available from Molecular Probes bind to cell membranes. Thus these FM membrane dyes may be used as general-purpose probes for endocytosis, because they are generally nontoxic. FM. . .

DETD . . . of these dyes. These two FM dyes have substantially nonoverlapping emission spectra. II) Test the affinity of FM dyes for microfluidic chips formed with PDMS, to define a background level of staining. III) Trap a Jurkat cell in a microfluidic chip and perform two-color staining of the cell using the two FM membrane dyes.

DETD [0829] Materials used for this analysis included the following. FM 1-43 and FM 4-64 were obtained from Molecular Probes. Microfluidic chips were produced based on system 250 of Example 2. Results were collected and recording using an inverted fluorescent microscope. . .

DETD [0838] Labeling of the microfluidic chip with the FM membrane dyes to determine background signal was carried out as follows.

DETD [0845] Cells were labeled with FM dyes in a microfluidic system as follows.

DETD [0846] Unlabeled Jurkat cells were loaded and captured in a microfluidic chip using PBS as a carrier buffer.

DETD [0858] Protocol B produced significant background labeling of microfluidic chips formed with PDMS, using either dye. The PDMS may be surface-modified to minimize binding of these dyes to the chip.

DETD [0859] Protocol C was foiled by the high background produced by dye binding to PDMS. After trapping a single cell in the chip, FM 1-43 bound to the chip more efficiently than to the membrane of the trapped cell.

DETD Capturing Cells in Single-Cell or Multi-Cell Microfluidic Chambers

DETD [0860] This example describes capture of a single cell or a cell population in a microfluidic system; see FIGS. 80-82.

DETD Fixing and Staining Cells in a Microfluidic System

DETD [0863] This example describes the use of a microfluidic system to fix a cell with an organic solvent, methanol, and label the cell with acridine orange; see FIG. 83.

DETD Microfluidic Mechanism for Measuring Cell Secretion

DETD [0865] This example describes the structure and use of a soft lithography-based, microfluidic system for measuring secretion of molecules, complexes, and/or small particles from cells.

DETD [0866] Many cell analyses measure release, and/or secretion of materials from cells. In some cases, the cells secrete material naturally. For example, neurons. . . cells for secretion of endocrine hormones, such as insulin, growth hormone, prolactin, steroid hormones, etc.; and a broad range of cell types for secretion of cytokines. In other cases, cells are lysed to define an aspect of their internal contents. However,. . . solution. Accordingly, such secreted or released materials may be difficult to analyze without concentrating them and/or without using immobilized, high-affinity binding partners, for example, in ELISA.

DETD [0867] Microfluidic systems may ameliorate some of the difficulties associated with measuring material released from cells, but may introduce additional considerations. In microfluidic systems, cells may be grown in isolated chambers having small volumes, as described above in Example 10. The chambers may. . . However, to maintain the released materials in a concentrated form, the chambers may be isolated from other portions of the microfluidic network. Such isolated chambers do not promote ready analysis of the released materials, since the materials may be isolated from analytical reagents and may be difficult to collect without substantially diluting the

released materials. Therefore, a microfluidic mechanism is needed that allows material released from cells to be collected and/or analyzed in a distinct fluidic compartment that is not part of a primary fluidic layer of a microfluidic system.

DETD [0868] This example provides a microfluidic system having a cell chamber and a separate material collection compartment that communicate fluidically through a semi-permeable membrane. The semi-permeable. . . in another compartment of the fluid layer, a compartment above the fluid layer, and/or below the substrate. For example, the microfluidic system may include a layer similar to the base layer of Example 11.

DETD Microfluidic Analysis of a Heterogeneous Particle Population--Part II

DETD [0869] This example describes microfluidic systems for sorting and analyzing heterogeneous populations of particles, such as blood samples, based on differences in particle size; see. . .

DETD [0871] This example provides a microfluidic system 1650 that selectively retains and analyzes larger particles from a mixture of larger and smaller particles; see FIGS. 84. . .

DETD . . . may functionally interconnect as follows. Input mechanism 1652 introduces particles from a particle sample placed in particle input-reservoir 1666, into microfluidic network 1668 of system 1650. Particles are moved by positioning mechanism 1654 to filtration mechanism 1656 by flow along inlet. . .

DETD [0878] System 1650 first separates white blood cells from smaller red blood cells and platelets. These separated white blood cells are directed to a retention site, retained, and then processed by the perfusion. . .

DETD . . . set of particle-selective channels or chamber channels 1704 also may be disposed around the perimeter of capture chamber 1706. Accordingly, red blood cells may travel to flow-through chambers 1708 and then waste reservoirs 1692, 1694, along a substantial area formed by inlet channel 1702 and chamber 1706. In particular, travel of red blood cells through particle-selective channels 1700 from inlet channel 1702 may avoid clogging chamber channels 1704. However, the white blood cells may. . .

DETD . . . Then, valve V2 may be opened to allow the carrying buffer provided by alternative input mechanism 1678 to wash residual red blood cells out of chamber 1706. At this point, waste reservoirs 1692, 1694 may be emptied to avoid reverse flow of the red blood cells back into chamber 1706.

DETD . . . plan view of a perfusion device for exposing particles to an array of different reagents or different reagent concentrations. Here, microfluidic passage device 2000 provides a plurality of growth/perfusion chambers 2030 for loading particles, such as cells, through loading passage 2010. . .

DETD . . . 94 depict a top plan view of a device being used to measure the response of cells to a chemo-attractant. Microfluidic passage device 2200 provides reagent loading chamber 2230, wherein reagent is metered into reagent chamber 2300 by the opening of. . .

CLM What is claimed is:

1. A microfluidic device for treating a particle comprising: (a) an input mechanism for introducing a fluid sample containing a particle; (b) a microfluidic passage in fluid communication with said input mechanism; (c) a positioning mechanism in fluid communication with said microfluidic passage, said positioning mechanism for positioning said particle in said microfluidic passage while contained in said fluid sample; (d) a retention mechanism for retaining said particle upon being positioned by said. . .

CLM What is claimed is:
2. The microfluidic device of claim 1 further comprising a release mechanism for releasing said particle from said retention mechanism.

CLM What is claimed is:
3. The microfluidic device of claim 2 further comprising an output mechanism for outputting said particle from said microfluidic device.

CLM What is claimed is:
4. The microfluidic device of claim 2 further comprising a cell culture mechanism for culturing said particle.

CLM What is claimed is:
5. The microfluidic device of claim 1 further comprising a control mechanism for determining aspects of the flow rate or path of the sample. . .
CLM What is claimed is:
6. The microfluidic device of claim 5, wherein said control mechanism is a valve in communication with said microfluidic passage.

CLM What is claimed is:
7. The microfluidic device of claim 6, wherein said microfluidic device is formed from a multi-layer elastomeric block and, wherein said valve is formed from an elastomeric membrane within said elastomeric. . .
CLM What is claimed is:
8. The microfluidic device of claim 6, wherein said control mechanism is a pump in communication with said microfluidic passage.

CLM What is claimed is:
9. The microfluidic device of claim 8, wherein said microfluidic device is formed from a multi-layer elastomeric block and, wherein said pump is formed from an elastomeric membrane within said elastomeric. . .
CLM What is claimed is:
10. The microfluidic device of claim 1, wherein said microfluidic device comprises a multi-layered elastomeric block having a control layer having an elastomeric membrane deflectable into said microfluidic passage in a fluidic layer to determine the flow rate or path of a fluid in said microfluidic passage.

CLM What is claimed is:
11. The microfluidic device of claim 1, wherein said microfluidic device comprises a layer including a material selected from the group consisting of elastomers, polydimethylsiloxane, plastic, polystyrene, polypropylene, polycarbonate, glass, ceramic,. . .
CLM What is claimed is:
12. The microfluidic device of claim 1, wherein said microfluidic passage has is less than about 500 micrometers wide.

CLM What is claimed is:
13. The microfluidic device of claim 1, wherein said microfluidic passage further comprises an adjacent passage joining said microfluidic passage at a junction or branch, said adjacent passage being selected from the group consisting of inlet

passage, outlet passage,. . .

CLM What is claimed is:
14. The microfluidic device of claim 13, wherein said adjacent passage is a dead-end passage.

CLM What is claimed is:
15. The microfluidic device of claim 13 further comprising said adjacent passage manipulating said particle.

CLM What is claimed is:
16. The microfluidic device of claim 15, wherein said particle manipulating is selected from the group of positioning, sorting, retaining, treating, detecting, propagating, storing,. . .

CLM What is claimed is:
17. The microfluidic device of claim 1, wherein said particle is selected from the group consisting of cells, eukaryotic cells, prokaryotic cells, plant cells,. . .

CLM What is claimed is:
18. The microfluidic device of claim 17, wherein said particle is a plurality or an aggregate of particles.

CLM What is claimed is:
19. The microfluidic device of claim 18, wherein said plurality of particles is a complex mixture containing different particles.

CLM What is claimed is:
20. The microfluidic device of claim 19, wherein said complex mixture containing different particles is whole blood or serum or bodily fluid.

CLM What is claimed is:
21. The microfluidic device of claim 1, wherein said particle is an egg or embryo.

CLM What is claimed is:
22. The microfluidic device of claim 1, wherein the input mechanism is a receptacle or well in fluid communication with said microfluidic passage.

CLM What is claimed is:
23. The microfluidic device of claim 22, wherein the input mechanism has a volume greater than a volume defined by said microfluidic passage.

CLM What is claimed is:
24. The microfluidic device of claim 1 further comprising a facilitating mechanism in communication with or acting upon said input mechanism.

CLM What is claimed is:
25. The microfluidic device of claim 24, wherein said facilitating mechanism is selected from the group consisting of gravity, fluid pressure, centrifugal pressure, pump. . .

CLM What is claimed is:
26. The microfluidic device of claim 1, wherein said positioning mechanism is a direct positioning mechanism or an indirect positioning mechanism.

CLM What is claimed is:
27. The microfluidic device of claim 26, wherein said direct positioning mechanism is a force selected from the group

consisting of optical, electrical, magnetic,. . .

CLM What is claimed is:
28. The microfluidic device of claim 27, wherein said electrical force is selected from the group consisting of electrophoretic, electroosmotic, electroendoosmotic, and dielectrophoretic.

CLM What is claimed is:
29. The microfluidic device of claim 26, wherein said indirect positioning mechanism is a longitudinal indirect positioning mechanism or a transverse indirect positioning mechanism. . . .

CLM What is claimed is:
30. The microfluidic device of claim 29, wherein said indirect positioning mechanism is facilitated by a pump or a valve associated with said microfluidic device.

CLM What is claimed is:
31. The microfluidic device of claim 29, wherein said transverse indirect positioning mechanism is facilitated by a fluid flow stream at a passage junction,. . .

CLM What is claimed is:
32. The microfluidic device of claim 31, wherein said passage junction is unifying or dividing.

CLM What is claimed is:
33. The microfluidic device of claim 29, wherein said transverse indirect positioning mechanism is a laminar flow-based transverse positioning means.

CLM What is claimed is:
34. The microfluidic device of claim 29, wherein said transverse indirect positioning mechanism is a stochastic transverse positioning mechanism.

CLM What is claimed is:
35. The microfluidic device of claim 34, wherein said stochastic transverse positioning mechanism randomly selects said particle from a population of particles by lateral. . .

CLM What is claimed is:
36. The microfluidic device of claim 29, wherein said transverse indirect positioning mechanism is a centrifugal forced-based transverse positioning mechanism.

CLM What is claimed is:
37. The microfluidic device of claim 1 wherein said retention mechanism selectively retains said particle at a pre-selected region within said microfluidic device.

CLM What is claimed is:
38. The microfluidic device of claim 37, wherein said retention mechanism retains said particle by overcoming or counteracting a force caused by said positioning. . .

CLM What is claimed is:
39. The microfluidic device of claim 1, wherein said retention mechanism is a trap or barrier-based retention mechanism.

CLM What is claimed is:
40. The microfluidic device of claim 39, wherein said barrier-based retention mechanism is restricts longitudinal movement of said particle in or adjacent said microfluidic passage.

CLM What is claimed is:
41. The microfluidic device of claim 38, wherein said retention mechanism is a protrusion extending, fixedly or transiently, into or adjacent said microfluidic passage to restrict longitudinal movement of said particle.

CLM What is claimed is:
42. The microfluidic device of claim 26, wherein said direct positioning mechanism is a chemical retention mechanism.

CLM What is claimed is:
43. The microfluidic device of claim 42, wherein said chemical retention mechanism is based on a specific affinity between said particle and said retention. . .

CLM What is claimed is:
44. The microfluidic device of claim 1, wherein said treatment mechanism is a fluid-mediated mechanism or a non-fluid mediated mechanism.

CLM What is claimed is:
45. The microfluidic device of claim 1, wherein said treatment mechanism exposes said particle to a reagent or physical condition.

CLM What is claimed is:
46. The microfluidic device of claim 45, wherein said reagent is selected from the group consisting of chemical modulator, biological modulator, agonist, antagonist, hormone,. . .

CLM What is claimed is:
47. The microfluidic device of claim 46, wherein said reagent attracts or repels said particles.

CLM What is claimed is:
48. The microfluidic device of claim 45, wherein said reagent induces or inhibits cell particle proliferation.

CLM What is claimed is:
49. The microfluidic device of claim 45, wherein said reagent is cytotoxic.

CLM What is claimed is:
50. The microfluidic device of claim 44, wherein said fluid-mediated mechanism further comprises a fluid treatment and wherein said particles are introduced to said. . .

CLM What is claimed is:
51. The microfluidic device of claim 44, wherein said fluid-mediated mechanism functions in conjunction with the functioning of said positioning mechanism.

CLM What is claimed is:
52. The microfluidic device of claim 51, wherein said positioning mechanism is a transverse positioning mechanism for moving said particle into and out of. . .

CLM What is claimed is:
53. The microfluidic device of claim 45, wherein said physical condition is selected from the group consisting of heat, light, radiation, sub-atomic particles, electric. . .

CLM What is claimed is:
54. The microfluidic device of claim 1, wherein said measurement mechanism is a detector associated with said microfluidic device that detects a characteristic of

said particle or caused by said particle.

CLM What is claimed is:
55. The microfluidic device of claim 54, wherein said detector is selected from the group consisting of spectroscopes, electronic sensors, hydrodynamic sensors, imaging systems,. . .

CLM What is claimed is:
56. The microfluidic device of claim 54, wherein said detector detects multiple values.

CLM What is claimed is:
57. The microfluidic device of claim 54, wherein said detector employs a detection mode that is selected from the group consisting of time-independent, time-dependent,. . .

CLM What is claimed is:
58. The microfluidic device of claim 54, wherein said detector is a spectroscopic detector that detects a signal produced of a type selected from. . .

CLM What is claimed is:
59. The microfluidic device of claim 54, wherein said detector is an electrical detector capable of detecting a signal selected from the group consisting. . .

CLM What is claimed is:
60. The microfluidic device of claim 54, wherein said detector is a hydrodynamic detector which detects a hydrodynamic interaction between said particle and a fluid, another particle, or said microfluidic passage.

CLM What is claimed is:
61. The microfluidic device of claim 60, wherein said interaction included a hydrodynamic interaction selected from the group consisting of chromatography, sedimentation, viscometry, electrophoresis.
. . .

CLM What is claimed is:
62. The microfluidic device of claim 54, wherein said detector is an imaging detector for creating and analyzing images of said particle(s).

CLM What is claimed is:
63. The microfluidic device of claim 54, wherein said detector detects a biological response produced by said particle(s).

CLM What is claimed is:
64. The microfluidic device of claim 63, wherein said biological response is selected from the group consisting of chemotaxis, biotaxis, senescence, apoptosis, proliferation, differentiation,. . .

CLM What is claimed is:
65. The microfluidic device of claim 1, further comprising a detection site, wherein said particle or product of said particle, is detected by said. . .

CLM What is claimed is:
66. The microfluidic device of claim 65, wherein said detection site is within said microfluidic device
.

CLM What is claimed is:
67. The microfluidic device of claim 65, wherein said detection site is located external to said microfluidic device.

CLM What is claimed is:
68. The microfluidic device of claim 54, wherein said detector detects a characteristic of said particle, directly or indirectly, said characteristic being selected from. . .

CLM What is claimed is:
69. The microfluidic device of claim 2, wherein said release mechanism operates by removing a retaining force caused by said retaining mechanism.

CLM What is claimed is:
70. The microfluidic device of claim 2, wherein said release mechanism operates by overcoming a retaining force caused by said retaining mechanism.

CLM What is claimed is:
71. The microfluidic device of claim 2, wherein said release mechanism operates by rendering ineffective a retaining force caused by said retaining mechanism.

CLM What is claimed is:
72. The microfluidic device of claim 2, further comprising directing said particle to another region within or external said microfluidic device.

CLM What is claimed is:
73. The microfluidic device of claim 72, wherein said another region is selected from the group consisting of a second positioning mechanism, a second. . .

CLM What is claimed is:
74. The microfluidic device of claim 73, wherein said second retention mechanism is a cell culture chamber.

CLM What is claimed is:
75. The microfluidic device of claim 3, further comprising said output mechanism outputting said particle to a location selected from the group consisting of. . .

CLM What is claimed is:
76. A method for perfusing cells with a reagent comprising the steps of: (a) providing a microfluidic device having (i) a cell growth chamber, a cell inlet in communication with said chamber, said cell inlet having an in. . .

CLM What is claimed is:
77. A method for treating a particle comprising the steps of: (i) providing a microfluidic device comprising: (a) an input mechanism for introducing a fluid sample containing a particle; (b) a microfluidic passage in fluid communication with said input mechanism; (c) a positioning mechanism in fluid communication with said microfluidic passage, said positioning mechanism for positioning said particle in said microfluidic passage while contained in said fluid sample; (d) a retention mechanism for retaining said particle upon being positioned by said. . .

CLM What is claimed is:
78. The method of claim 77 wherein said microfluidic device further comprises a release mechanism for releasing said particle from said retention mechanism, and said method further comprises the step. . .

CLM What is claimed is:
79. The method of claim 78, wherein said microfluidic device further comprises an output mechanism for outputting said particle from said microfluidic device, and said method further comprises the step of outputting said particle from said

microfluidic device by said output mechanism.

CLM What is claimed is:
80. The method of claim 78, wherein said microfluidic device further comprises a cell culture mechanism for culturing said particle, and the method further comprises the step of culturing said. . .

CLM What is claimed is:
81. The method of claim 77, wherein said microfluidic device further comprises a control mechanism for determining aspects of the flow rate or path of the sample fluid or other. . .

CLM What is claimed is:
82. The method of claim 81, wherein said control mechanism is a valve in communication with said microfluidic passage, and the method further comprises valving said sample fluid or other fluid with said valve.

CLM What is claimed is:
83. The microfluidic device of claim 82, wherein said microfluidic device is formed from a multi-layer elastomeric block and, wherein said valve is formed from an elastomeric membrane within said elastomeric block, and wherein said valving occurs by deflecting said elastomeric membrane into said microfluidic passage.

CLM What is claimed is:
84. The method of claim 82, wherein said control mechanism is a pump in communication with said microfluidic passage, and wherein said determining the flow rate or path of said sample fluid occurs by actuation of said pump.
. . .

CLM What is claimed is:
85. The method of claim 84, wherein said microfluidic device is formed from a multi-layer elastomeric block and, wherein said pump is formed from an elastomeric membrane within said elastomeric block, and wherein said pump is actuated by deflecting a series of elastomeric membranes into said microfluidic passage in a selected sequence.

CLM What is claimed is:
86. The method of claim 77, wherein said microfluidic device comprises a multi-layered elastomeric block having a control layer having an elastomeric membrane deflectable into said microfluidic passage in a fluidic layer to selectively determine the flow rate or path of a fluid in said microfluidic passage.

CLM What is claimed is:
87. The method of claim 77, wherein said microfluidic passage further comprises an adjacent passage joining said microfluidic passage at a junction or branch, said adjacent passage being selected from the group consisting of inlet passage, outlet passage,. . .

CLM What is claimed is:
. . . 96. The method of claim 77, wherein the input mechanism is a receptacle or well in fluid communication with said microfluidic passage, and said method further comprises the step of introducing said fluid sample into said receptacle.

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INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,

AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 17:52:32 ON 26 MAY 2008

SEA MICROFLUIDIC AND RED BLOOD CELLS

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4 FILE TOXCENTER
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25 FILE WPINDEX

L1 QUE MICROFLUIDIC AND RED BLOOD CELLS

SEA CELL(P)SIZE AND CELL(P)BIND? AND L1

0* FILE ADISNEWS
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0* FILE BIOENG
0* FILE BIOTECHABS
0* FILE BIOTECHDS
0* FILE BIOTECHNO
2 FILE CAPLUS
0* FILE CEABA-VTB
0* FILE CIN
0* FILE ESBIOBASE
0* FILE FOMAD
0* FILE FOREGE
0* FILE FROSTI
0* FILE FSTA
18 FILE IFIPAT
0* FILE KOSMET
1 FILE MEDLINE
0* FILE NTIS
0* FILE NUTRACEUT
0* FILE PASCAL
0* FILE PHARMAML
255 FILE USPATFULL
49 FILE USPAT2
0* FILE WATER
3 FILE WPIDS
3 FILE WPINDEX

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L2              QUE CELL(P) SIZE AND CELL(P) BIND? AND L1
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     FILE 'CAPLUS, IFIPAT, MEDLINE, USPATFULL, USPAT2' ENTERED AT 17:56:56 ON
     26 MAY 2008
L3          325 S L2
L4          259 DUP REM L3 (66 DUPLICATES REMOVED)
L5          163 S L4 AND ENRICH?
L6            0 S L5 AND HIST
L7          163 S L5 AND BIND?
L8           70 S L7 AND OBSTACLE?
L9            0 S L8 AND BINDING TO OBSTACLE?
L10          19 S L8 AND MICROFLUIDIC DEVICE

=> s l10 and cell binding
L11           5 L10 AND CELL BINDING

=> d l11 1-5

L11  ANSWER 1 OF 5  IFIPAT  COPYRIGHT 2008 IFI on STN
AN    11614553  IFIPAT;IFIUDB;IFICDB
TI    MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES
      THEREOF
IN    Kapur Ravi; Toner Mehmet; Truskey George
PA    General Hospital Corp The (10301)
PI    US 2007264675   A1  20071115
AI    US 2007-800940      20070508
RLI   US 2005-529453      20051219 CONTINUATION          PENDING
PRAI  US 2002-414065P     20020927 (Provisional)
      US 2002-414102P     20020927 (Provisional)
      US 2002-414258P     20020927 (Provisional)
FI    US 2007264675       20071115
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
ED    Entered STN: 16 Nov 2007
      Last Updated on STN: 13 Dec 2007
CLMN  27
GI     25 Figure(s).
     FIG. 1 is a schematic layout of a microfluidic device
      that enables selective lysis of cells.
     FIG. 2 is an illustration of the channel layout for the introduction of
      three fluids to the device, e.g., blood sample, lysis buffer, and
      diluent.
     FIG. 3 is an illustration of a repeating unit of the reaction chamber of
      the device where a sample of cells is passively mixed with a lysis
      buffer. In one example, 133 units are connected to form the reaction
      chamber.
     FIG. 4 is an illustration of the outlet channels of the device.
     FIG. 5 is an illustration of a device for cell lysis.
     FIGS. 6A and 6B are illustrations of a method for the fabrication of a
      device of the invention.
     FIG. 7 is a schematic diagram of a cell binding
      device.
     FIG. 8 is an exploded view of a cell binding device.
     FIG. 9 is an illustration of obstacles in a cell
      binding device.
     FIG. 10 is an illustration of types of obstacles.
     FIG. 11A is a schematic representation of a square array of
      obstacles. The square array has a capture efficiency of 40%. FIG.
      11B is a schematic representation of an equilateral triangle array of
      obstacles. The equilateral triangle array has a capture
```

efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

FIG. 18 is an illustration of a method of fabricating a cell binding device.

FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L11 ANSWER 2 OF 5 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11609304 IFIPAT;IFIUDB;IFICDB

TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007259424 A1 20071108
AI US 2007-726231 20070321
RLI US 2005-529453 20051219 DIVISION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007259424 20071108
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 14 Nov 2007
Last Updated on STN: 13 Dec 2007
CLMN 34
GI 25 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

FIG. 7 is a schematic diagram of a cell binding device.

FIG. 8 is an exploded view of a cell binding device.

FIG. 9 is an illustration of obstacles in a cell binding device.

FIG. 10 is an illustration of types of obstacles.

FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50

mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 1 6B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

FIG. 18 is an illustration of a method of fabricating a cell binding device.

FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L11 ANSWER 3 OF 5 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11581736 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007231851 A1 20071004
AI US 2007-726276 20070321
RLI US 2005-529453 20051219 CONTINUATION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007231851 20071004
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 8 Oct 2007
Last Updated on STN: 9 Nov 2007
CLMN 32
GI 25 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of

three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

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FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

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FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%. FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.339 l. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

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FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.
FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.
FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells
.
Figures are not necessarily to scale.

L11 ANSWER 4 OF 5 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11522821 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 2007172903 A1 20070726
AI US 2007-726230 20070321
RLI US 2005-529453 20051219 DIVISION PENDING
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2007172903 20070726
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 26 Jul 2007
Last Updated on STN: 16 Aug 2007
CLMN 44
GI 25 Figure(s).
FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.
FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.
FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.
FIG. 4 is an illustration of the outlet channels of the device.
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FIG. 8 is an exploded view of a cell binding device.
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FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array. FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop. FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr. FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.

FIG. 18 is an illustration of a method of fabricating a cell binding device.

FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.

FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series. FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.

FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.

FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention. FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation. FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells

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L11 ANSWER 5 OF 5 IFIPAT COPYRIGHT 2008 IFI on STN
AN 11185565 IFIPAT;IFIUDB;IFICDB
TI MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES

THEREOF
IN Kapur Ravi; Toner Mehmet; Truskey George
PA Unassigned Or Assigned To Individual (68000)
PPA General Hospital Corp The (Probable)
PI US 2006134599 A1 20060622
AI US 2003-529453 20030929
WO 2003-US30965 20030929
20051219 PCT 371 date
20051219 PCT 102(e) date
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 2006134599 20060622
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 24 Jun 2006
Last Updated on STN: 24 Jun 2006
CLMN 69
GI 32 Figure(s).

FIG. 1 is a schematic layout of a microfluidic device that enables selective lysis of cells.

FIG. 2 is an illustration of the channel layout for the introduction of three fluids to the device, e.g., blood sample, lysis buffer, and diluent.

FIG. 3 is an illustration of a repeating unit of the reaction chamber of the device where a sample of cells is passively mixed with a lysis buffer. In one example, 133 units are connected to form the reaction chamber.

FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

FIGS. 6A and 6B are illustrations of a method for the fabrication of a device of the invention.

FIG. 7 is a schematic diagram of a cell binding device.

FIG. 8 is an exploded view of a cell binding device.

FIG. 9 is an illustration of obstacles in a cell binding device.

FIG. 10 is an illustration of types of obstacles.

FIG. 11A is a schematic representation of a square array of obstacles. The square array has a capture efficiency of 40%.

FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array.

FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop.

FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of

98%.
FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr.
FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.
FIG. 17 is an illustration of various views of the inlet and outlets of a cell binding device.
FIG. 18 is an illustration of a method of fabricating a cell binding device.
FIG. 19 is an illustration of a mixture of cells flowing through a cell binding device.
FIG. 20A is an illustration of a cell binding device for trapping different types of cells in series.
FIG. 20B is an illustration of a cell binding device for trapping different types of cells in parallel.
FIG. 21 is an illustration of a cell binding device that enables recovery of bound cells.
FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention.
FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.
FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.
FIG. 24A is an illustration of a device for size based separation.
FIG. 24B is an electron micrograph of a device for size based separation.
FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells
.

```
=> s L10 and device
L12         19 L10 AND DEVICE

=> s l12 and device comprising obstacle?
L13          1 L12 AND DEVICE COMPRISING OBSTACLE?

=> d

L13  ANSWER 1 OF 1  IFIPAT  COPYRIGHT 2008 IFI on STN
AN    11185565  IFIPAT;IFIUDB;IFICDB
TI    MICROFLUIDIC DEVICE FOR CELL SEPARATION AND USES
      THEREOF
IN    Kapur Ravi; Toner Mehmet; Truskey George
PA    Unassigned Or Assigned To Individual (68000)
PPA   General Hospital Corp The (Probable)
PI    US 2006134599   A1  20060622
```

AI US 2003-529453 20030929
    WO 2003-US30965 20030929
                     20051219 PCT 371 date
                     20051219 PCT 102(e) date
PRAI US 2002-414065P 20020927 (Provisional)
    US 2002-414102P 20020927 (Provisional)
    US 2002-414258P 20020927 (Provisional)
FI US 2006134599 20060622
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
ED Entered STN: 24 Jun 2006
    Last Updated on STN: 24 Jun 2006
CLMN 69
GI 32 Figure(s).

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FIG. 4 is an illustration of the outlet channels of the device.

FIG. 5 is an illustration of a device for cell lysis.

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FIG. 11B is a schematic representation of an equilateral triangle array of obstacles. The equilateral triangle array has a capture efficiency of 56%.

FIG. 12A is a schematic representation of the calculation of the hydrodynamic efficiency for a square array.

FIG. 12B is a schematic representation of the calculation of the hydrodynamic efficiency for a diagonal array

FIGS. 13A-13B are graphs of the hydrodynamic (13A) and overall efficiency (13B) for square array and triangular array for a pressure drop of 150 Pa/m. This pressure drop corresponds to a flow rate of 0.75 mL/hr in the planar geometry.

FIG. 14A is a graph of the overall efficiency as a function of pressure drop.

FIG. 14B is a graph of the effect of the obstacle separation on the average velocity.

FIG. 15 is a schematic representation of the arrangement of obstacles for higher efficiency capture for an equilateral triangular array of obstacles in a staggered array. The capture radius rcap2=0.3391. The obstacles are numbered such that the first number refers to the triangle number and the second number refers to the triangle vertex. The staggered array has a capture efficiency of 98%.

FIG. 16A is a graph of the percent capture of cells as a function of the flow rate for a 100 mu m diameter obstacle geometry with a 50 mu m edge-to-edge spacing. The operating flow regime was established

across multiple cell types: cancer cells, normal connective tissue cells, and maternal and fetal samples. An optimal working flow regime is at 2.5 ml/hr.

FIG. 16B is a graph of the percent capture of cells as a function of the ratio of targets cells to white blood cells. The model system was generated by spiking defined number of either cancer cells, normal connective tissue cells, or cells from cord blood into defined number of cells from buffy coat of adult blood. The ratio of the contaminating cells to target cells was incrementally increased 5 log with as few as 10 target cells in the mixture. Yield was computed as the difference between number of spiked target cells captured on posts and number of cells spiked into the sample.

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FIG. 22A is an optical micrograph of fetal red blood cells adhered to an obstacle of the invention.

FIG. 22B is a fluorescent micrograph showing the results of a FISH analysis of a fetal red blood cell attached to an obstacle of the invention. FIG. 22C is a close up micrograph of FIG. 22B showing the individual hybridization results for the fetal red blood cell.

FIG. 23 is an illustration of a cell binding device in which beads trapped in a hydrogel are used to capture cells.

FIG. 24A is an illustration of a device for size based separation.

FIG. 24B is an electron micrograph of a device for size based separation.

FIG. 25 is a schematic representation of a device of the invention for isolating and analyzing fetal red blood cells.

```
=> s l10 and array
L14         18 L10 AND ARRAY

=> s l14 and separation of cell?
L15          8 L14 AND SEPARATION OF CELL?

=> d l15 1-8

L15  ANSWER 1 OF 8  USPATFULL on STN
AN     2008:76951  USPATFULL
TI     DC-dielectrophoresis microfluidic apparatus, and applications
       of same
IN     Li, Dongqing, Antioch, TN, UNITED STATES
PA     Vanderbilt University, Nashville, TN, UNITED STATES (U.S. corporation)
PI     US 2008067068       A1  20080320
AI     US 2006-523782      A1  20060919 (11)
DT     Utility
FS     APPLICATION
LN.CNT 2209
```

INCL INCLM: 204/451.000
INCLS: 204/601.000
NCL NCLM: 204/451.000
NCLS: 204/601.000
IC IPCI C07K0001-26 [I,A]; C07K0001-00 [I,C*]; G01N0027-00 [I,A]
IPCR C07K0001-00 [I,C]; C07K0001-26 [I,A]; G01N0027-00 [I,C];
G01N0027-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 2 OF 8 USPATFULL on STN
AN 2007:68534 USPATFULL
TI System for size based separation and analysis
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley MT, MA, UNITED STATES
Huang, Lotion R., Brookline, MA, UNITED STATES
Barber, Tom, Cambridge, MA, UNITED STATES
Carvalho, Bruce, Watertown, MA, UNITED STATES
Gray, Darren, Brookline, MA, UNITED STATES
PI US 2007059781 A1 20070315
AI US 2005-229336 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2363
INCL INCLM: 435/007.210
INCLS: 435/287.200; 702/019.000
NCL NCLM: 435/007.210
NCLS: 435/287.200; 702/019.000
IC IPCI G01N0033-567 [I,A]; G06F0019-00 [I,A]; C12M0003-00 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; C12M0003-00 [I,C];
C12M0003-00 [I,A]; G06F0019-00 [I,C]; G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 3 OF 8 USPATFULL on STN
AN 2007:68527 USPATFULL
TI Kits for Prenatal Testing
IN Grisham, Michael, Richmond, VA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
PI US 2007059774 A1 20070315
AI US 2005-229037 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2316
INCL INCLM: 435/007.200
NCL NCLM: 435/007.200
IC IPCI G01N0033-567 [I,A]; G01N0033-53 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; G01N0033-53 [I,C];
G01N0033-53 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 4 OF 8 USPATFULL on STN
AN 2007:68473 USPATFULL
TI Business methods for prenatal Diagnosis
IN Grisham, Michael, Richmond, VA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Tompkins, Ron, Boston, MA, UNITED STATES
Schmidt, Martin, Reading, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059719 A1 20070315
AI US 2005-229332 A1 20050915 (11)
DT Utility
FS APPLICATION

LN.CNT 2356
INCL INCLM: 435/006.000
INCLS: 705/002.000
NCL NCLM: 435/006.000
NCLS: 705/002.000
IC IPCI C12Q0001-68 [I,A]; G06Q0050-00 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06Q0050-00 [I,C];
G06Q0050-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 5 OF 8 USPATFULL on STN
AN 2007:68472 USPATFULL
TI Systems and methods for enrichment of analytes
IN Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059718 A1 20070315
AI US 2005-229328 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2296
INCL INCLM: 435/006.000
INCLS: 435/069.100
NCL NCLM: 435/006.000
NCLS: 435/069.100
IC IPCI C12Q0001-68 [I,A]; C12P0021-06 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12P0021-06 [I,C];
C12P0021-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 6 OF 8 USPATFULL on STN
AN 2007:68470 USPATFULL
TI Methods for detecting fetal abnormality
IN Balis, Ulysses, Peabody, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
Walsh, John, Auburndale, MA, UNITED STATES
PI US 2007059716 A1 20070315
AI US 2005-228454 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2300
INCL INCLM: 435/006.000
INCLS: 702/020.000
NCL NCLM: 435/006.000
NCLS: 702/020.000
IC IPCI C12Q0001-68 [I,A]; G06F0019-00 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06F0019-00 [I,C];
G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15 ANSWER 7 OF 8 USPATFULL on STN
AN 2007:68437 USPATFULL
TI Veterinary diagnostic system
IN Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien R., Brookline, MA, UNITED STATES
Gray, Darren, Brookline, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 2007059683 A1 20070315
AI US 2005-229359 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2321

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INCL   INCLM: 435/005.000
       INCLS: 435/006.000; 435/007.200; 977/902.000; 977/924.000
NCL    NCLM:  435/005.000
       NCLS:  435/006.000; 435/007.200; 977/902.000; 977/924.000
IC     IPCI   C12Q0001-70 [I,A]; C12Q0001-68 [I,A]; G01N0033-567 [I,A];
              G01N0033-53 [I,A]
       IPCR   C12Q0001-70 [I,C]; C12Q0001-70 [I,A]; C12Q0001-68 [I,C];
              C12Q0001-68 [I,A]; G01N0033-53 [I,C]; G01N0033-53 [I,A];
              G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L15  ANSWER 8 OF 8  USPATFULL on STN
AN     2007:68434  USPATFULL
TI     System for cell enrichment
IN     Kapur, Ravi, Stoughton, MA, UNITED STATES
       Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
       Huang, Lotien R., Brookline, MA, UNITED STATES
PI     US 2007059680       A1  20070315
AI     US 2005-228462      A1  20050915 (11)
DT     Utility
FS     APPLICATION
LN.CNT 2356
INCL   INCLM: 435/004.000
       INCLS: 435/005.000; 435/287.100; 435/006.000
NCL    NCLM:  435/004.000
       NCLS:  435/005.000; 435/006.000; 435/287.100
IC     IPCI   C12Q0001-00 [I,A]; C12Q0001-70 [I,A]; C12Q0001-68 [I,A];
              C12M0003-00 [I,A]
       IPCR   C12Q0001-00 [I,C]; C12Q0001-00 [I,A]; C12M0003-00 [I,C];
              C12M0003-00 [I,A]; C12Q0001-68 [I,C]; C12Q0001-68 [I,A];
              C12Q0001-70 [I,C]; C12Q0001-70 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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     (FILE 'HOME' ENTERED AT 17:51:25 ON 26 MAY 2008)

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     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 17:52:32 ON 26 MAY 2008
               SEA MICROFLUIDIC AND RED BLOOD CELLS
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               9   FILE ANABSTR
               1   FILE ANTE
               8   FILE BIOENG
              28   FILE BIOSIS
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               1   FILE BIOTECHDS
               1   FILE BIOTECHNO
               3   FILE CABA
              57   FILE CAPLUS
               1   FILE CEABA-VTB
               7   FILE DISSABS
              31   FILE EMBASE
              25   FILE ESBIOBASE
              65   FILE IFIPAT
               8   FILE LIFESCI
              37   FILE MEDLINE
               1   FILE NTIS
              15   FILE PASCAL
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                1   FILE PHIN
                8   FILE PROMT
               66   FILE SCISEARCH
                4   FILE TOXCENTER
              580   FILE USPATFULL
              113   FILE USPAT2
               25   FILE WPIDS
               25   FILE WPINDEX
L1               QUE MICROFLUIDIC AND RED BLOOD CELLS
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                 SEA CELL(P)SIZE AND CELL(P)BIND? AND L1
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                 0*  FILE ADISNEWS
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                 0*  FILE AQUALINE
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                 0*  FILE PASCAL
                 0*  FILE PHARMAML
               255   FILE USPATFULL
                49   FILE USPAT2
                 0*  FILE WATER
                 3   FILE WPIDS
                 3   FILE WPINDEX
L2               QUE CELL(P) SIZE AND CELL(P) BIND? AND L1
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     FILE 'CAPLUS, IFIPAT, MEDLINE, USPATFULL, USPAT2' ENTERED AT 17:56:56 ON
     26 MAY 2008
L3           325 S L2
L4           259 DUP REM L3 (66 DUPLICATES REMOVED)
L5           163 S L4 AND ENRICH?
L6             0 S L5 AND HIST
L7           163 S L5 AND BIND?
L8            70 S L7 AND OBSTACLE?
L9             0 S L8 AND BINDING TO OBSTACLE?
L10           19 S L8 AND MICROFLUIDIC DEVICE
L11            5 S L10 AND CELL BINDING
L12           19 S L10 AND DEVICE
L13            1 S L12 AND DEVICE COMPRISING OBSTACLE?
L14           18 S L10 AND ARRAY
L15            8 S L14 AND SEPARATION OF CELL?

=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
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	ENTRY	SESSION
FULL ESTIMATED COST	125.05	130.02

STN INTERNATIONAL LOGOFF AT 18:06:43 ON 26 MAY 2008

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssspt189dxw

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	AUG 10	Time limit for inactive STN sessions doubles to 40 minutes
NEWS 3	AUG 18	COMPENDEX indexing changed for the Corporate Source (CS) field
NEWS 4	AUG 24	ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
NEWS 5	AUG 24	CA/CAplus enhanced with legal status information for U.S. patents
NEWS 6	SEP 09	50 Millionth Unique Chemical Substance Recorded in CAS REGISTRY
NEWS 7	SEP 11	WPIDS, WPINDEX, and WPIX now include Japanese FTERM thesaurus
NEWS 8	OCT 21	Derwent World Patents Index Coverage of Indian and Taiwanese Content Expanded
NEWS 9	OCT 21	Derwent World Patents Index enhanced with human translated claims for Chinese Applications and Utility Models
NEWS 10	NOV 23	Addition of SCAN format to selected STN databases
NEWS 11	NOV 23	Annual Reload of IFI Databases
NEWS 12	DEC 01	FRFULL Content and Search Enhancements
NEWS 13	DEC 01	DGENE, USGENE, and PCTGEN: new percent identity feature for sorting BLAST answer sets
NEWS 14	DEC 02	Derwent World Patent Index: Japanese FI-TERM thesaurus added
NEWS 15	DEC 02	PCTGEN enhanced with patent family and legal status display data from INPADOCDB
NEWS 16	DEC 02	USGENE: Enhanced coverage of bibliographic and sequence information
NEWS 17	DEC 21	New Indicator Identifies Multiple Basic Patent Records Containing Equivalent Chemical Indexing in CA/CAplus
NEWS 18	JAN 12	Match STN Content and Features to Your Information Needs, Quickly and Conveniently
NEWS 19	JAN 25	Annual Reload of MEDLINE database
NEWS 20	FEB 16	STN Express Maintenance Release, Version 8.4.2, Is Now Available for Download
NEWS 21	FEB 16	Derwent World Patents Index (DWPI) Revises Indexing of Author Abstracts
NEWS 22	FEB 16	New FASTA Display Formats Added to USGENE and PCTGEN
NEWS 23	FEB 16	INPADOCDB and INPAFAMDB Enriched with New Content

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                  and Features
 NEWS 24  FEB 16  INSPEC Adding Its Own IPC codes and Author's E-mail
                  Addresses

 NEWS EXPRESS FEBRUARY 15 10 CURRENT WINDOWS VERSION IS V8.4.2,
              AND CURRENT DISCOVER FILE IS DATED 15 JANUARY 2010.

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  products is prohibited and may result in loss of user privileges
  and other penalties.

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FILE 'HOME' ENTERED AT 23:48:05 ON 28 FEB 2010

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
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FULL ESTIMATED COST                                       0.22       0.22

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
       CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 23:48:23 ON 28 FEB 2010

63 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s microfluidic device and (post? or obstacle? or struct?) and channel and (bind?
or antibody) and blood
          1   FILE ANABSTR
          1   FILE BIOENG
          3   FILE BIOSIS
          1   FILE BIOTECHABS
          1   FILE BIOTECHDS
  13 FILES SEARCHED...
          5   FILE CAPLUS
  23 FILES SEARCHED...
          1   FILE EMBASE
         23   FILE IFIPAT
          1   FILE LIFESCI
  41 FILES SEARCHED...
          1   FILE MEDLINE
          1   FILE PASCAL
  45 FILES SEARCHED...
          1   FILE PROMT
          2   FILE SCISEARCH
          1   FILE TOXCENTER
        914   FILE USPATFULL
        182   FILE USPAT2
```

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  60 FILES SEARCHED...
           6   FILE WPIDS
           6   FILE WPINDEX

  18 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L1   QUE MICROFLUIDIC DEVICE AND (POST? OR OBSTACLE? OR STRUCT?) AND CHANNEL AN
       D (BIND? OR ANTIBODY) AND BLOOD

=> s l1 and bind?(p)cells
           0*  FILE ADISNEWS
           0*  FILE ANTE
           0*  FILE AQUALINE
           0*  FILE BIOENG
           0*  FILE BIOTECHABS
           0*  FILE BIOTECHDS
           0*  FILE BIOTECHNO
           1   FILE CAPLUS
           0*  FILE CEABA-VTB
           0*  FILE CIN
  17 FILES SEARCHED...
  23 FILES SEARCHED...
           0*  FILE FOMAD
           0*  FILE FROSTI
           0*  FILE FSTA
          13   FILE IFIPAT
           0*  FILE KOSMET
           0*  FILE NTIS
           0*  FILE PASCAL
  45 FILES SEARCHED...
         502   FILE USPATFULL
          98   FILE USPAT2
           0*  FILE WATER
           2   FILE WPIDS
           2   FILE WPINDEX

   6 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L2   QUE L1 AND BIND?(P)CELLS

=> s L2 and bind?(p)obstacle?
           0*  FILE ADISNEWS
           0*  FILE ANTE
           0*  FILE AQUALINE
           0*  FILE BIOENG
           0*  FILE BIOTECHABS
           0*  FILE BIOTECHDS
           0*  FILE BIOTECHNO
           1   FILE CAPLUS
           0*  FILE CEABA-VTB
           0*  FILE CIN
  19 FILES SEARCHED...
  23 FILES SEARCHED...
           0*  FILE FOMAD
           0*  FILE FROSTI
           0*  FILE FSTA
           6   FILE IFIPAT
           0*  FILE KOSMET
           0*  FILE NTIS
           0*  FILE PASCAL
  45 FILES SEARCHED...
          28   FILE USPATFULL
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          1   FILE USPAT2
          0*  FILE WATER
          2   FILE WPIDS
          2   FILE WPINDEX

   6 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L3   QUE L2 AND BIND?(P)OBSTACLE?

=> file caplus ifipat uspatfull uspat2
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   9.66       9.88

FILE 'CAPLUS' ENTERED AT 23:56:36 ON 28 FEB 2010
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FILE 'USPAT2' ENTERED AT 23:56:36 ON 28 FEB 2010
CA INDEXING COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l3
L4          36 L3

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5           30 DUP REM L4 (6 DUPLICATES REMOVED)

=> d l5 1-10

L5   ANSWER 1 OF 30  USPATFULL on STN
AN     2010:4416  USPATFULL
TI     Microfluidic Methods for Diagnostics and Cellular Analysis
IN     Lee, Luke P., Orinda, CA, UNITED STATES
       Di Carlo, Dino, Boston, MA, UNITED STATES
       Nevill, Joshua Tanner, El Cerrito, CA, UNITED STATES
PA     THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, OAKLAND, CA, UNITED STATES
       (U.S. corporation)
PI     US 20100003666      A1  20100107
AI     US 2006-990130      A1  20060818 (11)
       WO 2006-US32355         20060818
                               20090828  PCT 371 date
PRAI   US 2005-709574P         20050819 (60)
       US 2005-709593P         20050819 (60)
DT     Utility
FS     APPLICATION
LN.CNT 1288
INCL   INCLM: 435 5
       INCLS: 435/029.000; 435/287.100
NCL    NCLM:  435 5
       NCLS:  435/029.000; 435/287.100
IC     IPCI   C12Q0001-70 [I,A]; C12Q0001-02 [I,A]; C12M0001-34 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5   ANSWER 2 OF 30  USPATFULL on STN
```

AN 2009:319842 USPATFULL
TI MICROFLUIDIC SYSTEM AND METHOD FOR SORTING CELL CLUSTERS AND FOR THE CONTINUOUS ENCAPSULATION THEREOF FOLLOWING SORTING THEREOF
IN Le Vot, Sophie, Le Pont De Claix, FRANCE
Berthier, Jean, Meylan, FRANCE
Rivera, Florence, Meylan, FRANCE
PA Commissariat A L'Energie Atomique (non-U.S. corporation)
PI US 20090286300 A1 20091119
AI US 2009-437901 A1 20090508 (12)
PRAI FR 2008-2575 20080513
DT Utility
FS APPLICATION
LN.CNT 1133
INCL INCLM: 435/177.000
INCLS: 435/308.100
NCL NCLM: 435/177.000
NCLS: 435/308.100
IC IPCI C12N0011-02 [I,A]; C12N0011-00 [I,C*]; C12M0001-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 3 OF 30 USPATFULL on STN
AN 2009:239723 USPATFULL
TI Tagged Ligands For Enrichment of Rare Analytes From A Mixed Sample
IN Forsyth, Allyn, San Diego, CA, UNITED STATES
Barnes, Helen, San Diego, CA, UNITED STATES
PA CellPoint Diagnostics, Inc., Mountain View, CA, UNITED STATES (U.S. corporation)
PI US 20090215088 A1 20090827
AI US 2008-37077 A1 20080225 (12)
DT Utility
FS APPLICATION
LN.CNT 728
INCL INCLM: 435/072.300
INCLS: 435/177.000; 435/072.000; 435/287.200
NCL NCLM: 435/007.230
NCLS: 435/007.200; 435/177.000; 435/287.200
IC IPCI G01N0033-574 [I,A]; C12N0011-02 [I,A]; C12N0011-00 [I,C*]; C12M0001-00 [I,A]; G01N0033-53 [I,A]
IPCR G01N0033-574 [I,C]; G01N0033-574 [I,A]; C12M0001-00 [I,C]; C12M0001-00 [I,A]; C12N0011-00 [I,C]; C12N0011-02 [I,A]; G01N0033-53 [I,C]; G01N0033-53 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 4 OF 30 USPATFULL on STN
AN 2009:201752 USPATFULL
TI DIAGNOSIS OF FETAL ABNORMALITIES USING NUCLEATED RED BLOOD CELLS
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Bianchi, Diana, Charlestown, MA, UNITED STATES
Barber, Tom, Allston, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
PI US 20090181421 A1 20090716
AI US 2008-172158 A1 20080711 (12)
RLI Continuation-in-part of Ser. No. US 2005-228462, filed on 15 Sep 2005, PENDING Continuation-in-part of Ser. No. US 2005-324041, filed on 29 Dec 2005, PENDING
PRAI US 2005-703833P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 1483
INCL INCLM: 435/039.000
NCL NCLM: 435/039.000

IC IPCI C12Q0001-06 [I,A]
    IPCR C12Q0001-06 [I,C]; C12Q0001-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 5 OF 30 USPATFULL on STN
AN 2009:152139 USPATFULL
TI CELL SEPARATION USING MICROCHANNEL HAVING PATTERNED POSTS
IN Tang, Zhongliang, San Diego, CA, UNITED STATES
    Tsinberg, Pavel, Carlsbad, CA, UNITED STATES
    Bhatt, Ram S., San Diego, CA, UNITED STATES
PA BIOCEPT, INC., San Diego, CA, UNITED STATES (U.S. corporation)
PI US 20090136982 A1 20090528
AI US 2006-814276 A1 20060105 (11)
    WO 2006-US383   20060105
                        20081125 PCT 371 date
RLI Continuation-in-part of Ser. No. US 2005-38920, filed on 18 Jan 2005,
    PENDING
PRAI US 2005-678004P   20050504 (60)
DT Utility
FS APPLICATION
LN.CNT 1266
INCL INCLM: 435/029.000
      INCLS: 435/378.000; 435/308.100
NCL   NCLM: 435/029.000
      NCLS: 435/308.100; 435/378.000
IC IPCI C12Q0001-02 [I,A]; C12N0005-06 [I,A]; C12M0001-00 [I,A]
    IPCR C12Q0001-02 [I,C]; C12Q0001-02 [I,A]; C12M0001-00 [I,C];
          C12M0001-00 [I,A]; C12N0005-06 [I,C]; C12N0005-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 6 OF 30 USPATFULL on STN
AN 2008:130394 USPATFULL
TI SELECTION OF CELLS USING BIOMARKERS
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
    Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
    Wang, Zihua, Newton, MA, UNITED STATES
PI US 20080113358 A1 20080515
AI US 2007-830546 A1 20070730 (11)
PRAI US 2006-820778P   20060728 (60)
DT Utility
FS APPLICATION
LN.CNT 3370
INCL INCLM: 435 6
NCL   NCLM: 435/006.000
IC IPCI C12Q0001-68 [I,A]
    IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 7 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 1
AN 11614553 IFIPAT;IFIUDB;IFICDB
TI Microfluidic device for cell separation and uses
    thereof
IN Truskey George; Kapur Ravi; Toner Mehmet
PA General Hospital Corp The (10301)
PI US 20070264675 A1 20071115
AI US 2007-800940   20070508 (11)
RLI US 2005-529453   20051219 CONTINUATION   PENDING
PRAI US 2002-414065P   20020927 (Provisional)
    US 2002-414102P   20020927 (Provisional)
    US 2002-414258P   20020927 (Provisional)
FI US 20070264675   20071115
DT Utility; Patent Application - First Publication

FS CHEMICAL
    APPLICATION
ED Entered STN: 16 Nov 2007
    Last Updated on STN: 13 Dec 2007
CLMN 27

L5 ANSWER 8 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 2
AN 11609304 IFIPAT;IFIUDB;IFICDB
TI Microfluidic device for cell separation and uses
    thereof
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 20070259424 A1 20071108
AI US 2007-726231   20070321 (11)
RLI US 2005-529453   20051219 DIVISION   PENDING
PRAI US 2002-414065P   20020927 (Provisional)
    US 2002-414102P   20020927 (Provisional)
    US 2002-414258P   20020927 (Provisional)
FI US 20070259424   20071108
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
ED Entered STN: 14 Nov 2007
    Last Updated on STN: 13 Dec 2007
CLMN 34

L5 ANSWER 9 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 3
AN 11581736 IFIPAT;IFIUDB;IFICDB
TI Microfluidic device for cell separation and uses
    thereof
IN Truskey George; Kapur Ravi; Toner Mehmet
PA General Hospital Corp The (10301)
PI US 20070231851 A1 20071004
AI US 2007-726276   20070321 (11)
RLI US 2005-529453   20051219 CONTINUATION   PENDING
PRAI US 2002-414065P   20020927 (Provisional)
    US 2002-414102P   20020927 (Provisional)
    US 2002-414258P   20020927 (Provisional)
FI US 20070231851   20071004
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
ED Entered STN: 8 Oct 2007
    Last Updated on STN: 9 Nov 2007
CLMN 32

L5 ANSWER 10 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 4
AN 11522821 IFIPAT;IFIUDB;IFICDB
TI Microfluidic device for cell separation and uses
    thereof
IN Kapur Ravi; Toner Mehmet; Truskey George
PA General Hospital Corp The (10301)
PI US 20070172903 A1 20070726
AI US 2007-726230   20070321 (11)
RLI US 2005-529453   20051219 DIVISION   PENDING
PRAI US 2002-414065P   20020927 (Provisional)
    US 2002-414102P   20020927 (Provisional)
    US 2002-414258P   20020927 (Provisional)
FI US 20070172903   20070726
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION

ED Entered STN: 26 Jul 2007
    Last Updated on STN: 16 Aug 2007
CLMN 44

=> d l5 11-20

L5 ANSWER 11 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 5
AN 11376372 IFIPAT;IFIUDB;IFICDB
TI Devices and methods for enrichment and alteration of cells and other
    particles
IN Barber Thomas A; Carvalho Bruce L; Huang Lotien Richard; Kapur Ravi;
    Toner Mehmet; Vernucci Paul; Wang Zihua
PA Unassigned Or Assigned To Individual (68000)
PI US 20070026381 A1 20070201
AI US 2006-449149   20060608 (11)
RLI WO 2006-US12820   20060405 CONTINUATION   PENDING
PRAI US 2005-668415P   20050405 (Provisional)
    US 2005-704067P   20050729 (Provisional)
FI US 20070026381   20070201
DT Utility; Patent Application - First Publication
FS CHEMICAL
    APPLICATION
ED Entered STN: 2 Feb 2007
    Last Updated on STN: 20 Mar 2007
CLMN 116

L5 ANSWER 12 OF 30 USPATFULL on STN
AN 2007:224722 USPATFULL
TI Devices and methods for enrichment and alteration of cells and other
    particles
IN Kapur, Ravi, UNITED STATES
    Toner, Mehmet, UNITED STATES
PI US 20070196820   A1 20070823
AI US 2005-227904   A1 20050915 (11)
PRAI US 2005-668415P   20050405 (60)
    US 2005-704067P   20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 2442
INCL INCLM: 435/005.000
    INCLS: 435/007.210; 435/287.200
NCL NCLM: 435/005.000
    NCLS: 435/007.210; 435/287.200
IC IPCI C12Q0001-70 [I,A]; G01N0033-567 [I,A]; C12M0003-00 [I,A]
    IPCR C12Q0001-70 [I,C]; C12Q0001-70 [I,A]; C12M0003-00 [I,C];
          C12M0003-00 [I,A]; G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 13 OF 30 USPATFULL on STN
AN 2007:184063 USPATFULL
TI Device for cell separation and analysis and method of using
IN Tsinberg, Pavel, Carlsbad, CA, UNITED STATES
    Tang, Zhongliang, San Diego, CA, UNITED STATES
PA Biocept, Inc., San Diego, CA, UNITED STATES (U.S. corporation)
PI US 20070161051   A1 20070712
AI US 2006-331988   A1 20060112 (11)
DT Utility
FS APPLICATION
LN.CNT 959
INCL INCLM: 435/007.200
    INCLS: 435/287.200

NCL NCLM: 435/007.200
NCLS: 435/287.200
IC IPCI G01N0033-567 [I,A]; C12M0001-34 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; C12M0001-34 [I,C];
C12M0001-34 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 14 OF 30 USPATFULL on STN
AN 2007:114136 USPATFULL
TI Devices and methods for enrichment and alteration of circulating tumor cells and other particles
IN Fuchs, Martin, Uxbridge, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Huang, Yi-Shuian, Taipei, TAIWAN, PROVINCE OF CHINA
Krueger, Neil X., Jamaica Plain, MA, UNITED STATES
Haber, Daniel A., Newton, MA, UNITED STATES
PI US 20070099207 A1 20070503
AI US 2006-449161 A1 20060608 (11)
RLI Continuation of Ser. No. WO 2006-US12778, filed on 5 Apr 2006, PENDING Continuation-in-part of Ser. No. US 2005-323962, filed on 29 Dec 2005, PENDING Continuation-in-part of Ser. No. US 2005-323946, filed on 29 Dec 2005, PENDING Continuation-in-part of Ser. No. US 2005-323945, filed on 29 Dec 2005, PENDING Continuation-in-part of Ser. No. US 2005-322790, filed on 29 Dec 2005, PENDING Continuation-in-part of Ser. No. US 2005-324041, filed on 29 Dec 2005, PENDING
PRAI US 2005-668415P 20050405 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 8534
INCL INCLM: 435/006.000
INCLS: 435/007.230
NCL NCLM: 435/006.000
NCLS: 435/007.230
IC IPCI C12Q0001-68 [I,A]; G01N0033-574 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G01N0033-574 [I,C];
G01N0033-574 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 15 OF 30 USPATFULL on STN
AN 2007:68534 USPATFULL
TI System for size based separation and analysis
IN Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley MT, MA, UNITED STATES
Huang, Lotion R., Brookline, MA, UNITED STATES
Barber, Tom, Cambridge, MA, UNITED STATES
Carvalho, Bruce, Watertown, MA, UNITED STATES
Gray, Darren, Brookline, MA, UNITED STATES
PI US 20070059781 A1 20070315
AI US 2005-229336 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2363
INCL INCLM: 435/007.210
INCLS: 435/287.200; 702/019.000
NCL NCLM: 435/007.210
NCLS: 435/287.200; 702/019.000
IC IPCI G01N0033-567 [I,A]; G06F0019-00 [I,A]; C12M0003-00 [I,A]

IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; C12M0003-00 [I,C];
C12M0003-00 [I,A]; G06F0019-00 [I,C]; G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 16 OF 30 USPATFULL on STN
AN 2007:68527 USPATFULL
TI Kits for Prenatal Testing
IN Grisham, Michael, Richmond, VA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
PI US 20070059774 A1 20070315
AI US 2005-229037 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2316
INCL INCLM: 435/007.200
NCL NCLM: 435/007.200
IC IPCI G01N0033-567 [I,A]; G01N0033-53 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; G01N0033-53 [I,C];
G01N0033-53 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 17 OF 30 USPATFULL on STN
AN 2007:68473 USPATFULL
TI Business methods for prenatal Diagnosis
IN Grisham, Michael, Richmond, VA, UNITED STATES
Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Tompkins, Ron, Boston, MA, UNITED STATES
Schmidt, Martin, Reading, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 20070059719 A1 20070315
AI US 2005-229332 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2356
INCL INCLM: 435/006.000
INCLS: 705/002.000
NCL NCLM: 435/006.000
NCLS: 705/002.000
IC IPCI C12Q0001-68 [I,A]; G06Q0050-00 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06Q0050-00 [I,C];
G06Q0050-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 18 OF 30 USPATFULL on STN
AN 2007:68472 USPATFULL
TI Systems and methods for enrichment of analytes
IN Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 20070059718 A1 20070315
AI US 2005-229328 A1 20050915 (11)
DT Utility
FS APPLICATION
LN.CNT 2296
INCL INCLM: 435/006.000
INCLS: 435/069.100
NCL NCLM: 435/006.000
NCLS: 435/069.100
IC IPCI C12Q0001-68 [I,A]; C12P0021-06 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12P0021-06 [I,C];
C12P0021-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

```
L5   ANSWER 19 OF 30  USPATFULL on STN
AN     2007:68470  USPATFULL
TI     Methods for detecting fetal abnormality
IN     Balis, Ulysses, Peabody, MA, UNITED STATES
       Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
       Kapur, Ravi, Stoughton, MA, UNITED STATES
       Walsh, John, Auburndale, MA, UNITED STATES
PI     US 20070059716      A1  20070315
AI     US 2005-228454      A1  20050915 (11)
DT     Utility
FS     APPLICATION
LN.CNT 2300
INCL   INCLM: 435/006.000
       INCLS: 702/020.000
NCL    NCLM:  435/006.000
       NCLS:  702/020.000
IC     IPCI   C12Q0001-68 [I,A]; G06F0019-00 [I,A]
       IPCR   C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G06F0019-00 [I,C];
              G06F0019-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5   ANSWER 20 OF 30  USPATFULL on STN
AN     2007:68437  USPATFULL
TI     Veterinary diagnostic system
IN     Barber, Tom, Cambridge, MA, UNITED STATES
       Huang, Lotien R., Brookline, MA, UNITED STATES
       Gray, Darren, Brookline, MA, UNITED STATES
       Kapur, Ravi, Stoughton, MA, UNITED STATES
PI     US 20070059683      A1  20070315
AI     US 2005-229359      A1  20050915 (11)
DT     Utility
FS     APPLICATION
LN.CNT 2321
INCL   INCLM: 435/005.000
       INCLS: 435/006.000; 435/007.200; 977/902.000; 977/924.000
NCL    NCLM:  435/005.000
       NCLS:  435/006.000; 435/007.200; 977/902.000; 977/924.000
IC     IPCI   C12Q0001-70 [I,A]; C12Q0001-68 [I,A]; G01N0033-567 [I,A];
              G01N0033-53 [I,A]
       IPCR   C12Q0001-70 [I,C]; C12Q0001-70 [I,A]; C12Q0001-68 [I,C];
              C12Q0001-68 [I,A]; G01N0033-53 [I,C]; G01N0033-53 [I,A];
              G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d 21-30

L5   ANSWER 21 OF 30  USPATFULL on STN
AN     2007:68434  USPATFULL
TI     System for cell enrichment
IN     Kapur, Ravi, Stoughton, MA, UNITED STATES
       Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
       Huang, Lotien R., Brookline, MA, UNITED STATES
PI     US 20070059680      A1  20070315
AI     US 2005-228462      A1  20050915 (11)
DT     Utility
FS     APPLICATION
LN.CNT 2356
INCL   INCLM: 435/004.000
       INCLS: 435/005.000; 435/287.100; 435/006.000
NCL    NCLM:  435/004.000
```

NCLS: 435/005.000; 435/006.000; 435/287.100
IC IPCI C12Q0001-00 [I,A]; C12Q0001-70 [I,A]; C12Q0001-68 [I,A]; C12M0003-00 [I,A]
IPCR C12Q0001-00 [I,C]; C12Q0001-00 [I,A]; C12M0003-00 [I,C]; C12M0003-00 [I,A]; C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12Q0001-70 [I,C]; C12Q0001-70 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 22 OF 30 USPATFULL on STN
AN 2007:30145 USPATFULL
TI Devices and methods for enrichment and alteration of circulating tumor cells and other particles
IN Fuchs, Martin, Uxbridge, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Huang, Yi-Shuian, Roslindale, MA, UNITED STATES
Krueger, Neil X., Jamaica Plain, MA, UNITED STATES
Wang, Ying-Xin, Newtonville, MA, UNITED STATES
PI US 20070026415 A1 20070201
AI US 2005-323946 A1 20051229 (11)
PRAI US 2005-703833P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 3773
INCL INCLM: 435/006.000
INCLS: 435/007.200; 435/287.200
NCL NCLM: 435/006.000
NCLS: 435/007.200; 435/287.200
IC IPCI C12Q0001-68 [I,A]; G01N0033-567 [I,A]; C12M0001-34 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12M0001-34 [I,C]; C12M0001-34 [I,A]; G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 23 OF 30 IFIPAT COPYRIGHT 2010 IFI on STN DUPLICATE 6
AN 11185565 IFIPAT;IFIUDB;IFICDB
TI Microfluidic device for cell separation and uses thereof
IN Kapur Ravi; Toner Mehmet; Truskey George
PA Unassigned Or Assigned To Individual (68000)
PPA General Hospital Corp The (Probable)
PI US 20060134599 A1 20060622
AI US 2003-529453 20030929 (10)
WO 2003-US30965 20030929
20051219 PCT 371 date
20051219 PCT 102(e) date
PRAI US 2002-414065P 20020927 (Provisional)
US 2002-414102P 20020927 (Provisional)
US 2002-414258P 20020927 (Provisional)
FI US 20060134599 20060622
DT Utility; Patent Application - First Publication
FS CHEMICAL
APPLICATION
ED Entered STN: 24 Jun 2006
Last Updated on STN: 24 Jun 2006
CLMN 69

L5 ANSWER 24 OF 30 USPATFULL on STN
AN 2006:261665 USPATFULL
TI Devices and methods for magnetic enrichment of cells and other particles
IN Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien Richard, Brookline, MA, UNITED STATES
Schmidt, Martin, Reading, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES

Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 20060223178 A1 20061005
AI US 2005-323971 A1 20051229 (11)
RLI Continuation-in-part of Ser. No. US 2005-227904, filed on 15 Sep 2005, PENDING
PRAI US 2005-668415P 20050405 (60)
US 2005-704067P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 3051
INCL INCLM: 435/325.000
INCLS: 435/372.000
NCL NCLM: 435/325.000
NCLS: 435/372.000
IC IPCI C12N0005-08 [I,A]; C12N0005-00 [I,A]
IPCR C12N0005-08 [I,C]; C12N0005-08 [I,A]; C12N0005-00 [I,C]; C12N0005-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 25 OF 30 USPATFULL on STN
AN 2006:208847 USPATFULL
TI Closed-system multi-stage nucleic acid amplification reactions
IN Ching, Jesus, San Jose, CA, UNITED STATES
Chang, Ronald, Redwood City, CA, UNITED STATES
Dority, Douglas Bryan, Mill Valley, CA, UNITED STATES
Zhang, Jian Ping, Moraga, CA, UNITED STATES
Wang, James Jian Quan, Fremont, CA, UNITED STATES
Wong, Wendy Wingkei, Mountain View, CA, UNITED STATES
Paul, Kendra Lara, Santa Clara, CA, UNITED STATES
Van Atta, Reuel, Palo Alto, CA, UNITED STATES
PA Cepheid, Sunnyvale, CA, UNITED STATES (U.S. corporation)
PI US 20060177844 A1 20060810
AI US 2005-262523 A1 20051027 (11)
PRAI US 2004-622393P 20041027 (60)
DT Utility
FS APPLICATION
LN.CNT 2281
INCL INCLM: 435/006.000
INCLS: 435/091.200
NCL NCLM: 435/006.000
NCLS: 435/091.200
IC IPCI C12Q0001-68 [I,A]; C12P0019-34 [I,A]; C12P0019-00 [I,C*]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 26 OF 30 USPATFULL on STN
AN 2005:305794 USPATFULL
TI Magnetic device for isolation of cells and biomolecules in a microfluidic environment
IN Kapur, Ravi, Boston, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Carvalho, Bruce L., Watertown, MA, UNITED STATES
Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien R., Brookline, MA, UNITED STATES
PI US 20050266433 A1 20051201
AI US 2005-71679 A1 20050303 (11)
PRAI US 2004-549610P 20040303 (60)
DT Utility
FS APPLICATION
LN.CNT 740
INCL INCLM: 435/006.000
INCLS: 435/287.200; 435/007.100
NCL NCLM: 435/006.000

NCLS: 435/007.100; 435/287.200
IC [7]
ICM C12Q001-68
ICS G01N033-53; C12M001-34
IPCI C12Q0001-68 [ICM,7]; G01N0033-53 [ICS,7]; C12M0001-34 [ICS,7]
IPCR B01L0003-00 [N,C*]; B01L0003-00 [N,A]; C12M0001-34 [I,C*]; C12M0001-34 [I,A]; C12Q0001-68 [I,C*]; C12Q0001-68 [I,A]; G01N0033-53 [I,C*]; G01N0033-53 [I,A]; G01N0033-543 [I,C*]; G01N0033-543 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2010 ACS on STN
AN 2004:292081 CAPLUS
DN 140:283937
TI Microfluidic device for cell separation and uses thereof
IN Toner, Mehmet; Truskey, George; Kapur, Ravi
PA The General Hospital Corporation, USA; GPB Scientific LLC
SO PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004029221	A2	20040408	WO 2003-US30965	20030929
	WO 2004029221	A3	20040513		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	CA 2500392	A1	20040408	CA 2003-2500392	20030929
	AU 2003277153	A1	20040419	AU 2003-277153	20030929
	EP 1569510	A2	20050907	EP 2003-798803	20030929
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	JP 2006501449	T	20060112	JP 2004-540301	20030929
	US 20060134599	A1	20060622	US 2005-529453	20051219
	US 20070172903	A1	20070726	US 2007-726230	20070321
	US 20070231851	A1	20071004	US 2007-726276	20070321
	US 20070259424	A1	20071108	US 2007-726231	20070321
	US 20070264675	A1	20071115	US 2007-800940	20070508
PRAI	US 2002-414065P	P	20020927		
	US 2002-414102P	P	20020927		
	US 2002-414258P	P	20020927		
	WO 2003-US30965	W	20030929		
	US 2005-529453	A3	20051219		

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 30 USPAT2 on STN
AN 2002:48270 USPAT2
TI Methods for analyzing protein binding events
IN Hefti, John, San Francisco, CA, United States

PA Signature BioScience, Inc., San Francisco, CA, United States (U.S. corporation)
PI US 6566079 B2 20030520
AI US 2001-923474 20010806 (9)
RLI Continuation of Ser. No. US 1999-365580, filed on 2 Aug 1999, now patented, Pat. No. US 6287874 Continuation of Ser. No. US 1999-243194, filed on 1 Feb 1999, now patented, Pat. No. US 6368795
PRAI US 1998-73445P 19980202 (60)
US 1999-134740P 19990518 (60)
DT Utility
FS GRANTED
LN.CNT 4076
INCL INCLM: 435/007.100
INCLS: 435/287.100; 436/501.000; 436/086.000; 436/149.000
NCL NCLM: 506/009.000; 435/006.000
NCLS: 435/007.100; 435/287.100; 436/086.000; 436/149.000; 436/501.000; 506/012.000; 435/007.210; 436/071.000
IC [7]
ICM G01N033-53
ICS G01N033-566; G01N033-00; G01N025-18; C12M001-34; C12M003-00
IPCI C12Q0001-68 [ICM,7]; G01N0033-53 [ICS,7]; G01N0033-567 [ICS,7]; G01N0033-92 [ICS,7]
IPCI-2 G01N0033-53 [ICM,7]; G01N0033-566 [ICS,7]; G01N0033-00 [ICS,7]; G01N0025-18 [ICS,7]; C12M0001-34 [ICS,7]; C12M0003-00 [ICS,7]
IPCR C12Q0001-00 [I,C*]; C12Q0001-00 [I,A]; G01N0033-543 [I,C*]; G01N0033-543 [I,A]
EXF 435/7.1; 435/287.1; 436/501; 436/86; 436/149
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 29 OF 30 USPATFULL on STN
AN 2002:48270 USPATFULL
TI Methods for analyzing protein binding events
IN Hefti, John J., San Francisco, CA, UNITED STATES
PI US 20020028461 A1 20020307
US 6566079 B2 20030520
AI US 2001-923474 A1 20010806 (9)
RLI Continuation of Ser. No. US 1999-365580, filed on 2 Aug 1999, GRANTED, Pat. No. US 6287874 Continuation-in-part of Ser. No. US 1999-243194, filed on 1 Feb 1999, PENDING
PRAI US 1998-73445P 19980202 (60)
US 1999-134740P 19990518 (60)
DT Utility
FS APPLICATION
LN.CNT 4041
INCL INCLM: 435/006.000
INCLS: 435/007.100; 435/007.210; 436/071.000
NCL NCLM: 506/009.000; 435/006.000
NCLS: 435/007.100; 435/287.100; 436/086.000; 436/149.000; 436/501.000; 506/012.000; 435/007.210; 436/071.000
IC [7]
ICM C12Q001-68
ICS G01N033-53; G01N033-567; G01N033-92
IPCI C12Q0001-68 [ICM,7]; G01N0033-53 [ICS,7]; G01N0033-567 [ICS,7]; G01N0033-92 [ICS,7]
IPCI-2 G01N0033-53 [ICM,7]; G01N0033-566 [ICS,7]; G01N0033-00 [ICS,7]; G01N0025-18 [ICS,7]; C12M0001-34 [ICS,7]; C12M0003-00 [ICS,7]
IPCR C12Q0001-00 [I,C*]; C12Q0001-00 [I,A]; G01N0033-543 [I,C*]; G01N0033-543 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 30 OF 30 USPATFULL on STN
AN 2001:152781 USPATFULL

```
TI     Methods for analyzing protein binding events
IN     Hefti, John, San Francisco, CA, United States
PA     Signature BioScience, Inc., Hayward, CA, United States (U.S.
       corporation)
PI     US 6287874          B1  20010911
AI     US 1999-365580          19990802 (9)
RLI    Continuation-in-part of Ser. No. US 1999-243194, filed on 1 Feb 1999
PRAI   US 1998-73445P          19980202 (60)
       US 1999-134740P         19990518 (60)
DT     Utility
FS     GRANTED
LN.CNT 4099
INCL   INCLM: 436/501.000
       INCLS: 436/086.000; 436/149.000
NCL    NCLM:  506/009.000
       NCLS:  436/086.000; 436/149.000; 436/501.000
IC     [7]
       ICM    G01N033-566
       ICS    G01N033-00; G01N025-18
       IPCI   G01N0033-566 [ICM,7]; G01N0033-00 [ICS,7]; G01N0025-18 [ICS,7]
       IPCR   C12Q0001-00 [I,A]; C12Q0001-00 [I,C*]; G01N0033-543 [I,A];
              G01N0033-543 [I,C*]; H01J0049-02 [I,C*]; H01J0049-04 [I,A]
EXF    435/6; 422/50; 422/82.01
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


=> d l5 30 ab

L5   ANSWER 30 OF 30  USPATFULL on STN
AB     The present invention provides a variety of methods of analyzing protein
       binding events using a system capable of directly detecting
       protein/ligand complexes based upon the dielectric properties of the
       complex. The system can be used in a variety of analyses involving
       protein binding events, such as screening ligand libraries,
       characterizing protein binding interactions, and identifying
       ligands. The system can also be utilized in diverse analytical and
       diagnostic applications.


=> s l5 and binding cells (to or with) obstacles
MISSING OPERATOR 'CELLS (TO'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l5 and binding to obstacles
L6           0 L5 AND BINDING TO OBSTACLES

=> s l5 and flow?
L7          29 L5 AND FLOW?

=> s l7 and blood
L8          29 L7 AND BLOOD

=> s l8 and enrich?
L9          27 L8 AND ENRICH?

=> s l9 and enriching(p)cells
L10         16 L9 AND ENRICHING(P) CELLS

=> s l9 and releas?(p)bound(p)cells
L11         10 L9 AND RELEAS?(P) BOUND(P) CELLS
```

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=> d l11 1-10

L11  ANSWER 1 OF 10  IFIPAT  COPYRIGHT 2010 IFI on STN
AN    11581736  IFIPAT;IFIUDB;IFICDB
TI    Microfluidic device for cell separation and uses
      thereof
IN    Truskey George; Kapur Ravi; Toner Mehmet
PA    General Hospital Corp The (10301)
PI    US 20070231851  A1  20071004
AI    US 2007-726276      20070321  (11)
RLI   US 2005-529453      20051219 CONTINUATION          PENDING
PRAI  US 2002-414065P      20020927 (Provisional)
      US 2002-414102P      20020927 (Provisional)
      US 2002-414258P      20020927 (Provisional)
FI    US 20070231851      20071004
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
ED    Entered STN: 8 Oct 2007
      Last Updated on STN: 9 Nov 2007
CLMN  32

L11  ANSWER 2 OF 10  IFIPAT  COPYRIGHT 2010 IFI on STN
AN    11185565  IFIPAT;IFIUDB;IFICDB
TI    Microfluidic device for cell separation and uses
      thereof
IN    Kapur Ravi; Toner Mehmet; Truskey George
PA    Unassigned Or Assigned To Individual (68000)
PPA   General Hospital Corp The (Probable)
PI    US 20060134599  A1  20060622
AI    US 2003-529453      20030929  (10)
      WO 2003-US30965     20030929
                          20051219  PCT 371 date
                          20051219  PCT 102(e) date
PRAI  US 2002-414065P      20020927 (Provisional)
      US 2002-414102P      20020927 (Provisional)
      US 2002-414258P      20020927 (Provisional)
FI    US 20060134599      20060622
DT    Utility; Patent Application - First Publication
FS    CHEMICAL
      APPLICATION
ED    Entered STN: 24 Jun 2006
      Last Updated on STN: 24 Jun 2006
CLMN  69

L11  ANSWER 3 OF 10  USPATFULL on STN
AN     2009:152139  USPATFULL
TI     CELL SEPARATION USING MICROCHANNEL HAVING PATTERNED POSTS
IN     Tang, Zhongliang, San Diego, CA, UNITED STATES
       Tsinberg, Pavel, Carlsbad, CA, UNITED STATES
       Bhatt, Ram S., San Diego, CA, UNITED STATES
PA     BIOCEPT, INC., San Diego, CA, UNITED STATES (U.S. corporation)
PI     US 20090136982      A1  20090528
AI     US 2006-814276      A1  20060105 (11)
       WO 2006-US383           20060105
                               20081125  PCT 371 date
RLI    Continuation-in-part of Ser. No. US 2005-38920, filed on 18 Jan 2005,
       PENDING
PRAI   US 2005-678004P         20050504 (60)
DT     Utility
FS     APPLICATION
LN.CNT 1266
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INCL INCLM: 435/029.000
      INCLS: 435/378.000; 435/308.100
NCL   NCLM: 435/029.000
      NCLS: 435/308.100; 435/378.000
IC   IPCI   C12Q0001-02 [I,A]; C12N0005-06 [I,A]; C12M0001-00 [I,A]
      IPCR   C12Q0001-02 [I,C]; C12Q0001-02 [I,A]; C12M0001-00 [I,C];
             C12M0001-00 [I,A]; C12N0005-06 [I,C]; C12N0005-06 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 4 OF 10 USPATFULL on STN
AN   2008:130394 USPATFULL
TI   SELECTION OF CELLS USING BIOMARKERS
IN   Kapur, Ravi, Stoughton, MA, UNITED STATES
      Toner, Mehmet, Wellesley Hills, MA, UNITED STATES
      Wang, Zihua, Newton, MA, UNITED STATES
PI   US 20080113358   A1 20080515
AI   US 2007-830546   A1 20070730 (11)
PRAI US 2006-820778P   20060728 (60)
DT   Utility
FS   APPLICATION
LN.CNT 3370
INCL INCLM: 435 6
NCL   NCLM: 435/006.000
IC   IPCI   C12Q0001-68 [I,A]
      IPCR   C12Q0001-68 [I,C]; C12Q0001-68 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 5 OF 10 USPATFULL on STN
AN   2007:224722 USPATFULL
TI   Devices and methods for enrichment and alteration of cells and
      other particles
IN   Kapur, Ravi, UNITED STATES
      Toner, Mehmet, UNITED STATES
PI   US 20070196820   A1 20070823
AI   US 2005-227904   A1 20050915 (11)
PRAI US 2005-668415P   20050405 (60)
      US 2005-704067P   20050729 (60)
DT   Utility
FS   APPLICATION
LN.CNT 2442
INCL INCLM: 435/005.000
      INCLS: 435/007.210; 435/287.200
NCL   NCLM: 435/005.000
      NCLS: 435/007.210; 435/287.200
IC   IPCI   C12Q0001-70 [I,A]; G01N0033-567 [I,A]; C12M0003-00 [I,A]
      IPCR   C12Q0001-70 [I,C]; C12Q0001-70 [I,A]; C12M0003-00 [I,C];
             C12M0003-00 [I,A]; G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 6 OF 10 USPATFULL on STN
AN   2007:184063 USPATFULL
TI   Device for cell separation and analysis and method of using
IN   Tsinberg, Pavel, Carlsbad, CA, UNITED STATES
      Tang, Zhongliang, San Diego, CA, UNITED STATES
PA   Biocept, Inc., San Diego, CA, UNITED STATES (U.S. corporation)
PI   US 20070161051   A1 20070712
AI   US 2006-331988   A1 20060112 (11)
DT   Utility
FS   APPLICATION
LN.CNT 959
INCL INCLM: 435/007.200
      INCLS: 435/287.200

NCL NCLM: 435/007.200
NCLS: 435/287.200
IC IPCI G01N0033-567 [I,A]; C12M0001-34 [I,A]
IPCR G01N0033-567 [I,C]; G01N0033-567 [I,A]; C12M0001-34 [I,C];
C12M0001-34 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 7 OF 10 USPATFULL on STN
AN 2007:114136 USPATFULL
TI Devices and methods for enrichment and alteration of
circulating tumor cells and other particles
IN Fuchs, Martin, Uxbridge, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Huang, Yi-Shuian, Taipei, TAIWAN, PROVINCE OF CHINA
Krueger, Neil X., Jamaica Plain, MA, UNITED STATES
Haber, Daniel A., Newton, MA, UNITED STATES
PI US 20070099207 A1 20070503
AI US 2006-449161 A1 20060608 (11)
RLI Continuation of Ser. No. WO 2006-US12778, filed on 5 Apr 2006, PENDING
Continuation-in-part of Ser. No. US 2005-323962, filed on 29 Dec 2005,
PENDING Continuation-in-part of Ser. No. US 2005-323946, filed on 29 Dec
2005, PENDING Continuation-in-part of Ser. No. US 2005-323945, filed on
29 Dec 2005, PENDING Continuation-in-part of Ser. No. US 2005-322790,
filed on 29 Dec 2005, PENDING Continuation-in-part of Ser. No. US
2005-324041, filed on 29 Dec 2005, PENDING
PRAI US 2005-668415P 20050405 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
US 2005-703833P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 8534
INCL INCLM: 435/006.000
INCLS: 435/007.230
NCL NCLM: 435/006.000
NCLS: 435/007.230
IC IPCI C12Q0001-68 [I,A]; G01N0033-574 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G01N0033-574 [I,C];
G01N0033-574 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 8 OF 10 USPATFULL on STN
AN 2007:30145 USPATFULL
TI Devices and methods for enrichment and alteration of
circulating tumor cells and other particles
IN Fuchs, Martin, Uxbridge, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Huang, Yi-Shuian, Roslindale, MA, UNITED STATES
Krueger, Neil X., Jamaica Plain, MA, UNITED STATES
Wang, Ying-Xin, Newtonville, MA, UNITED STATES
PI US 20070026415 A1 20070201
AI US 2005-323946 A1 20051229 (11)
PRAI US 2005-703833P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 3773
INCL INCLM: 435/006.000
INCLS: 435/007.200; 435/287.200
NCL NCLM: 435/006.000
NCLS: 435/007.200; 435/287.200

IC IPCI C12Q0001-68 [I,A]; G01N0033-567 [I,A]; C12M0001-34 [I,A]
IPCR C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; C12M0001-34 [I,C];
C12M0001-34 [I,A]; G01N0033-567 [I,C]; G01N0033-567 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 9 OF 10 USPATFULL on STN
AN 2006:261665 USPATFULL
TI Devices and methods for magnetic enrichment of cells and other particles
IN Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien Richard, Brookline, MA, UNITED STATES
Schmidt, Martin, Reading, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Kapur, Ravi, Stoughton, MA, UNITED STATES
PI US 20060223178 A1 20061005
AI US 2005-323971 A1 20051229 (11)
RLI Continuation-in-part of Ser. No. US 2005-227904, filed on 15 Sep 2005, PENDING
PRAI US 2005-668415P 20050405 (60)
US 2005-704067P 20050729 (60)
DT Utility
FS APPLICATION
LN.CNT 3051
INCL INCLM: 435/325.000
INCLS: 435/372.000
NCL NCLM: 435/325.000
NCLS: 435/372.000
IC IPCI C12N0005-08 [I,A]; C12N0005-00 [I,A]
IPCR C12N0005-08 [I,C]; C12N0005-08 [I,A]; C12N0005-00 [I,C];
C12N0005-00 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 10 OF 10 USPATFULL on STN
AN 2005:305794 USPATFULL
TI Magnetic device for isolation of cells and biomolecules in a microfluidic environment
IN Kapur, Ravi, Boston, MA, UNITED STATES
Toner, Mehmet, Wellesley, MA, UNITED STATES
Carvalho, Bruce L., Watertown, MA, UNITED STATES
Barber, Tom, Cambridge, MA, UNITED STATES
Huang, Lotien R., Brookline, MA, UNITED STATES
PI US 20050266433 A1 20051201
AI US 2005-71679 A1 20050303 (11)
PRAI US 2004-549610P 20040303 (60)
DT Utility
FS APPLICATION
LN.CNT 740
INCL INCLM: 435/006.000
INCLS: 435/287.200; 435/007.100
NCL NCLM: 435/006.000
NCLS: 435/007.100; 435/287.200
IC [7]
ICM C12Q001-68
ICS G01N033-53; C12M001-34
IPCI C12Q0001-68 [ICM,7]; G01N0033-53 [ICS,7]; C12M0001-34 [ICS,7]
IPCR B01L0003-00 [N,C*]; B01L0003-00 [N,A]; C12M0001-34 [I,C*];
C12M0001-34 [I,A]; C12Q0001-68 [I,C*]; C12Q0001-68 [I,A];
G01N0033-53 [I,C*]; G01N0033-53 [I,A]; G01N0033-543 [I,C*];
G01N0033-543 [I,A]
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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=> d hist

     (FILE 'HOME' ENTERED AT 23:48:05 ON 28 FEB 2010)

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
     AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
     CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
     DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 23:48:23 ON 28 FEB 2010
               SEA MICROFLUIDIC DEVICE AND (POST? OR OBSTACLE? OR STRUCT?) AND
              ---------
              1   FILE ANABSTR
              1   FILE BIOENG
              3   FILE BIOSIS
              1   FILE BIOTECHABS
              1   FILE BIOTECHDS
              5   FILE CAPLUS
              1   FILE EMBASE
             23   FILE IFIPAT
              1   FILE LIFESCI
              1   FILE MEDLINE
              1   FILE PASCAL
              1   FILE PROMT
              2   FILE SCISEARCH
              1   FILE TOXCENTER
            914   FILE USPATFULL
            182   FILE USPAT2
              6   FILE WPIDS
              6   FILE WPINDEX
L1             QUE MICROFLUIDIC DEVICE AND (POST? OR OBSTACLE? OR STRUCT?) AND
              ---------
               SEA L1 AND BIND?(P)CELLS
              ---------
              0*  FILE ADISNEWS
              0*  FILE ANTE
              0*  FILE AQUALINE
              0*  FILE BIOENG
              0*  FILE BIOTECHABS
              0*  FILE BIOTECHDS
              0*  FILE BIOTECHNO
              1   FILE CAPLUS
              0*  FILE CEABA-VTB
              0*  FILE CIN
              0*  FILE FOMAD
              0*  FILE FROSTI
              0*  FILE FSTA
             13   FILE IFIPAT
              0*  FILE KOSMET
              0*  FILE NTIS
              0*  FILE PASCAL
            502   FILE USPATFULL
             98   FILE USPAT2
              0*  FILE WATER
              2   FILE WPIDS
              2   FILE WPINDEX
L2             QUE L1 AND BIND?(P)CELLS
              ---------
               SEA L2 AND BIND?(P)OBSTACLE?
              ---------
              0*  FILE ADISNEWS
              0*  FILE ANTE
              0*  FILE AQUALINE
              0*  FILE BIOENG
```

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                0*  FILE BIOTECHABS
                0*  FILE BIOTECHDS
                0*  FILE BIOTECHNO
                1   FILE CAPLUS
                0*  FILE CEABA-VTB
                0*  FILE CIN
                0*  FILE FOMAD
                0*  FILE FROSTI
                0*  FILE FSTA
                6   FILE IFIPAT
                0*  FILE KOSMET
                0*  FILE NTIS
                0*  FILE PASCAL
               28   FILE USPATFULL
                1   FILE USPAT2
                0*  FILE WATER
                2   FILE WPIDS
                2   FILE WPINDEX
L3               QUE L2 AND BIND?(P)OBSTACLE?
                 ---------

     FILE 'CAPLUS, IFIPAT, USPATFULL, USPAT2' ENTERED AT 23:56:36 ON 28 FEB
     2010
L4            36 S L3
L5            30 DUP REM L4 (6 DUPLICATES REMOVED)
L6             0 S L5 AND BINDING TO OBSTACLES
L7            29 S L5 AND FLOW?
L8            29 S L7 AND BLOOD
L9            27 S L8 AND ENRICH?
L10           16 S L9 AND ENRICHING(P)CELLS
L11           10 S L9 AND RELEAS?(P)BOUND(P)CELLS

=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 125.94     135.82

STN INTERNATIONAL LOGOFF AT 00:02:50 ON 01 MAR 2010
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